OES NOT CIRCULATE

58 Assembly — Interstate Postgraduate Medical Association — Cleveland — November 10-13

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Postgraduate Medicine

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• NEPHROTIC SYNDROME

Q. Localized swelling of the lower lid of the right eye recently developed in a five year old boy with glomerulonephritis. Later on the same day, his other eye and his ankles became swollen. Urinalysis has consistently revealed 4 plus protein, or over 300 mg. as indicated by the albumin test.

The patient was treated at home with 400 mg. BICILLIN® and 2 mg. MEDROL®, administered morning and evening. On about the fifth day of the treatment, diuresis was pronounced and the albumin decreased to 100 mg. Subsequently, he was given 1 mg. Medrol and 1 mg. penicillin morning and evening. Two weeks later, the child was hospitalized, because he would not stay in bed at home. On admission, the sedimentation rate was 41 mg., albumin 4 plus, and there were a few red blood cells and white blood cells in the urine. The white blood cell count was 13,000. For about five or six days, he had a little edema around his eyes but none in his ankles; his abdomen was slightly increased in size. Three or four days later, the sedimentation rate was 51 mg., dropping to 36 mg. the following day. The patient had oliguria with a daily output of urine below 500 cc., which decreased when the fluid intake was restricted to 500 cc. His weight was constant at 40 to 40½ lb., except for a few days when he gained 1½ lb. and his abdomen became quite prominent. His blood pressure has been around 72/54. When first seen, he had a slight cold and a temperature of 99.2° F., which disappeared in two or three days following administration of penicillin.

Bed rest is the only treatment I have found in the literature. May DIURIL®, a nonmercurial agent, be given to the patient since his abdomen now appears non-nephrotic? What is the proper dosage of Medrol or of a related corticosteroid compound for this patient? Would gamma globulin be beneficial? Since neither hematuria nor hypertension is present, what is the prognosis?

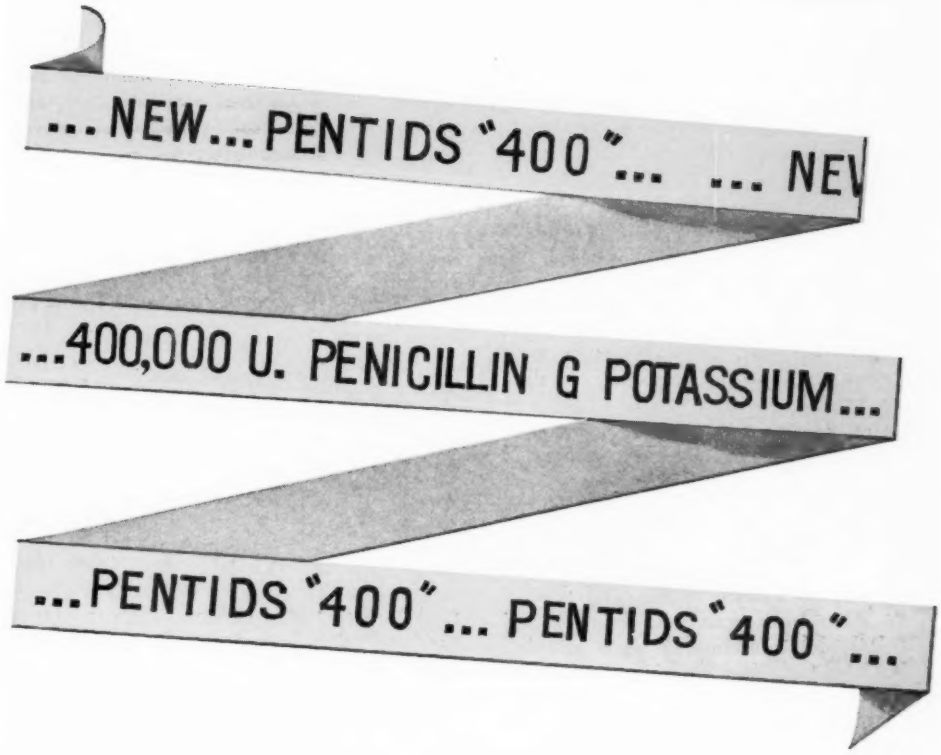
M.D.—Iowa

A. The history is typical of the nephrotic syndrome, and hematuria commonly occurs at some time during its course. Therefore, on this basis alone, the diagnosis does not change to chronic nephritis. The treatment of choice for nephrotic children is a program of continuous prophylactic administration of an antibiotic agent, usually penicillin, associated with intermittent steroid therapy. Chlorothiazide (Diuril) has been prescribed occasionally and has been variably successful. Rather than using Diuril for complete diuresis, some prefer to use it in conjunction with steroids in a "three days on, four days off" type of program as long as albuminuria persists. Of course, mercurial agents have no place in treating nephrosis. To induce diuresis, prednisone or prednisolone usually is administered in a dosage of 20 to 30 mg. daily on an intermittent program or 40 mg. per square meter per day for 8 to 10 days. The newer steroid hormones offer no decided advantages in treating nephrosis.

Administration of gamma globulin is fruitless during the albuminuric state of nephrosis, because this protein merely runs out through damaged glomerular walls into the urine with other proteins.

The prognosis for recovery is good. Present figures rather consistently show a five year survival rate of 70 per cent in a group of steroid-treated nephrotic patients. Another 10 or 15 years must elapse before it will be possible to say with certainty that steroids or antibiotics, or both, have materially improved the recovery rate in the nephrotic syndrome.

(Continued on page A-20)



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• MEATOTOMY PROCEDURE

Q. A 17 month old baby needs a meatotomy because of a very small opening in his penis. Since several different procedures can be employed in this operation, which type is the best and safest for a child of this age? One urologist has suggested cystoscopy as a precautionary measure, followed by a clamping technic to produce a necrosis. Is cystoscopy advisable?

M.D.—New York

A. I would suggest meatotomy by incision of the meatus and then sewing the mucosa of the urethra to the skin of the glans penis. Cystoscopy or intravenous urograms, or both, are necessary because other congenital anomalies are usually present, and the upper tract must be checked for pyelectasis and ureterectasis which may be present because of the obstruction of urine at the meatus.

• MANAGEMENT OF HEART DISEASE

Q. A 59 year old man has had chest pain since the fall of 1956. He had two coronary attacks in 1956 and possibly a third in the early part of 1957. An electrocardiogram revealed a healed myocardial septal infarction, a sinus and left bundle-branch block, and occasional premature ventricular systole. The patient's heart tones have the ticktock rhythm of arteriosclerosis and his blood pressure is consistently low, 94/70. A complete blood count was within normal limits, with hemoglobin 14.9 gm., red blood cell count 4,890,000, and white blood cell count 7700.

Since his cardiac attacks, he has been taking 2 to 5 mg. COUMADIN® sodium daily, and at present is taking 2.5 mg. five days a week. His prothrombin time is about 22 seconds, 32 per cent. He is also taking 10 mg. NEO-SYNEPHRINE® before arising and minimal doses of nitroglycerin.

The patient is apprehensive of any changes in this treatment, although he has gained in physical strength and seems well. How long should he continue taking Coumadin sodium and Neo-Synephrine?

M.D.—California

A. Since this patient is doing so well on the present medication, it seems unwise to change it. There is no contraindication to continuous use of Neo-Synephrine or Coumadin sodium as long as the prothrombin time is checked frequently.

• INDUCTION OF LABOR WITH OXYTOCIN

Q. I would appreciate an opinion regarding the use of an oxytocic pituitary extract in obstetrics. I am referring specifically to its use either intramuscularly or intravenously in the induction of labor, and its use during labor for uterine atony. Secondly, is there a possibility of uterine rupture if doses of 0.10 cc. of oxytocin are given every 15 to 20 minutes?

M.D.—Wisconsin

A. The induction of labor with oxytocin has been discussed in a comprehensive article (Elective induction of labor, Obst. & Gynec. 5:519-527 [April] 1955) by Dr. Edward H. Bishop, whose work has my complete endorsement.

In reference to the question on the danger of uterine rupture while using doses of 0.10 cc. of oxytocin every 15 or 20 minutes, I would emphasize that no patient should be given oxytocin either intravenously or intramuscularly unless disproportion and malposition have been ruled out. We feel that there is a distinct advantage in using the drug intravenously since its effect can be stopped immediately if there should be a tetanic contraction. When the drug is given intramuscularly, it must be completely absorbed before it ceases to be effective. After the possibility of disproportion and malposition has been eliminated, I can see no objection to using minimal doses intramuscularly if the obstetrician keeps the patient under close personal observation. His hand should be on her abdomen until the drug is no longer effective. The drug may be used in this way on a trial basis.

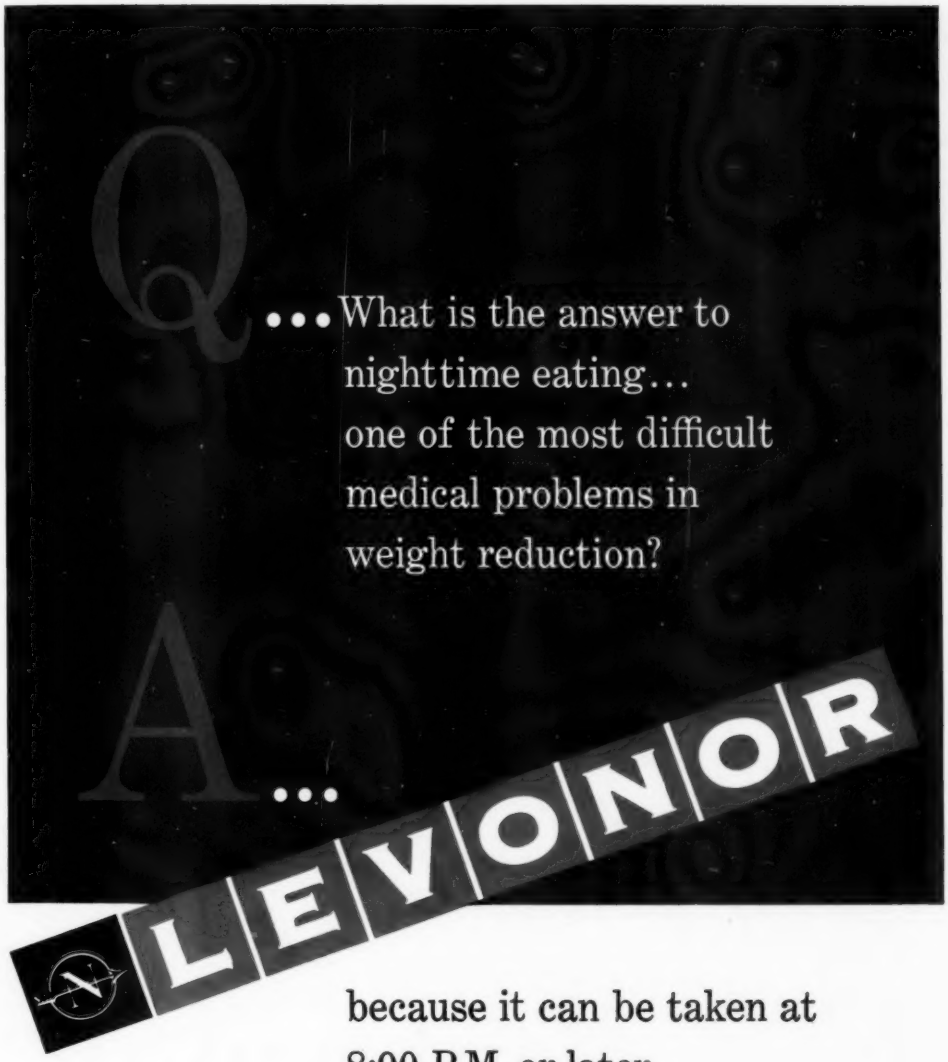
• AFTEREFFECTS OF FROZEN EARS

Q. A 48 year old man froze his ears 25 years ago. A few years later, a segment of the cartilage in the upper portion of the right pinna became very hard; apparently, it has calcified. This area frequently becomes very tender when the patient rubs or lies on the ear. What treatment would you advise?

M.D.—British Columbia

A. Interference with an area such as described is likely to result only in recurrent and increased symptoms. The patient should be advised to sleep on the opposite ear and to take every precaution against freezing the involved ear again.

(Continued on page A-22)



because it can be taken at
8:00 P.M. or later
without interfering
with sleep.

administration and dosage:
Average dose: 5 to 10 mg. twice daily.

how supplied:
Bottles of 100 tablets, each tablet containing 5 mg. of
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• UNUSUAL GROWTH OF HAIR

Q. An eight and one-half year old Caucasian boy wore a plaster of paris cast for three months. After removal of the cast, a profuse growth of dark hair covered the entire area. What is your opinion of this condition?

M.D.—Pennsylvania

A. I believe that time alone will take care of this abnormal growth of hair. The irritation is probably a stimulation to hair growth, and when it is gone the hair probably will become normal in color.

• SYPHILIS TESTS

Q. To my knowledge, the only tests that have recently been established for detection of syphilis are the *Treponema pallidum* immobilization and the darkfield illumination tests. Where may I find information on them?

M.D.—New York

A. Information on the treponemal immobilization test may be found in "The Year Book of Dermatology and Syphilology" (1956-1957 series), pages 337 through 339.

• LONG-TERM THERAPY IN TUBERCULOSIS

Q. A 68 year old man has been receiving injections of 1 gm. dihydrostreptomycin sulfate twice weekly and 16 tablets of para-amino sodium salicylate daily since November 1955. Three weeks ago, chest x-ray findings were normal. The patient was in a tuberculosis sanatorium before this series of injections was initiated. Should treatment be stopped or continued at this time?

M.D.—Michigan

A. Certain essential data would be desirable, including the original extent and character of the tuberculosis, the initial bacteriologic status, and the time at which conversion occurred. A completely normal x-ray finding is unusual in a patient who recently has had active pulmonary tuberculosis.

Toxicity to dihydrostreptomycin sulfate or PAS would have appeared much earlier and would not be anticipated at this time. Chemotherapy may be discontinued unless the tuberculosis was very advanced when first diagnosed. Continued observation at three month intervals is recommended.

(Continued on page A-24)

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DOSAGE: One to two tablets q.i.d., before mea's and on retiring.

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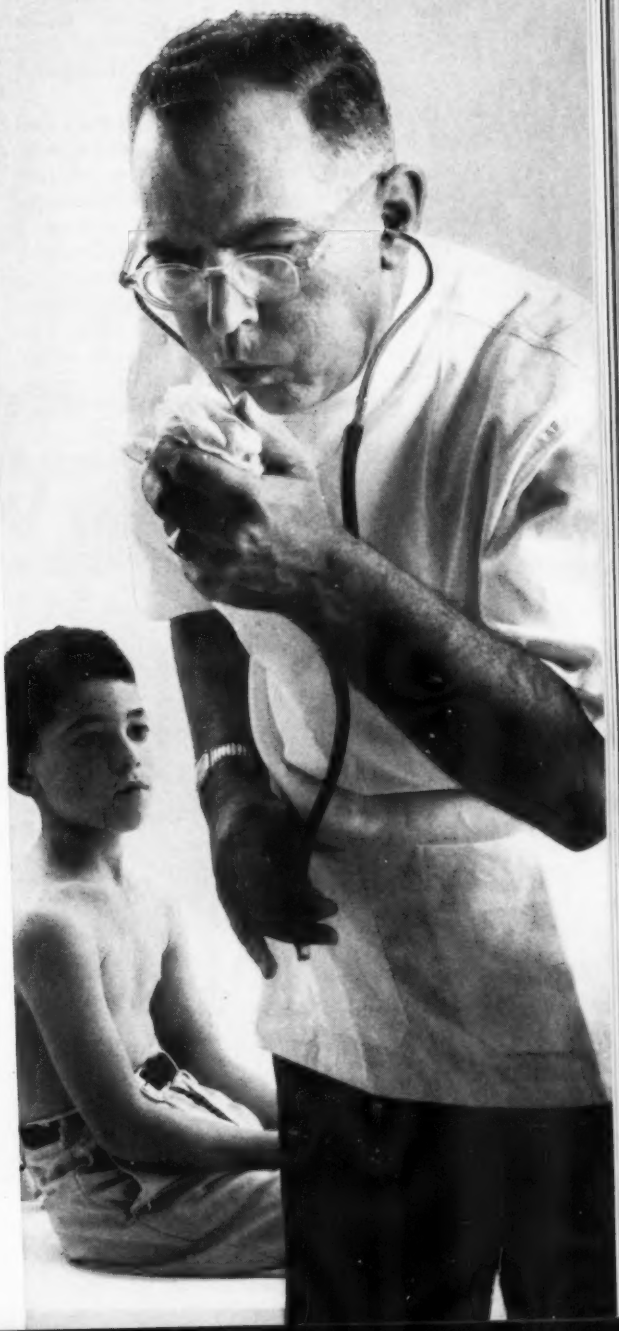


ROCHE

Romilar® Hydrobromide—brand of dextromethorphan hydrobromide

• MALE STERILITY

Q. Examination of semen from a 30 year old man in apparent good health gave the following results: (1) appearance and consistency—normal; (2) volume—7.4 cc.; (3) sperm count—86,000,000 per cubic centimeter; (4) degree of abnormality—55 per cent; (5) motility—50 per cent at one hour, 40 per cent at two hours, 25 per cent at three hours, 5 per cent at four hours, and none at five hours.

What may be done for this patient? Would he be considered sterile?

M.D.—Michigan

A. The method used for collection of the semen should first be considered since abnormal morphology may occur when specimens are collected by condom or in a vessel which is not chemically clean. A second examination should be done.

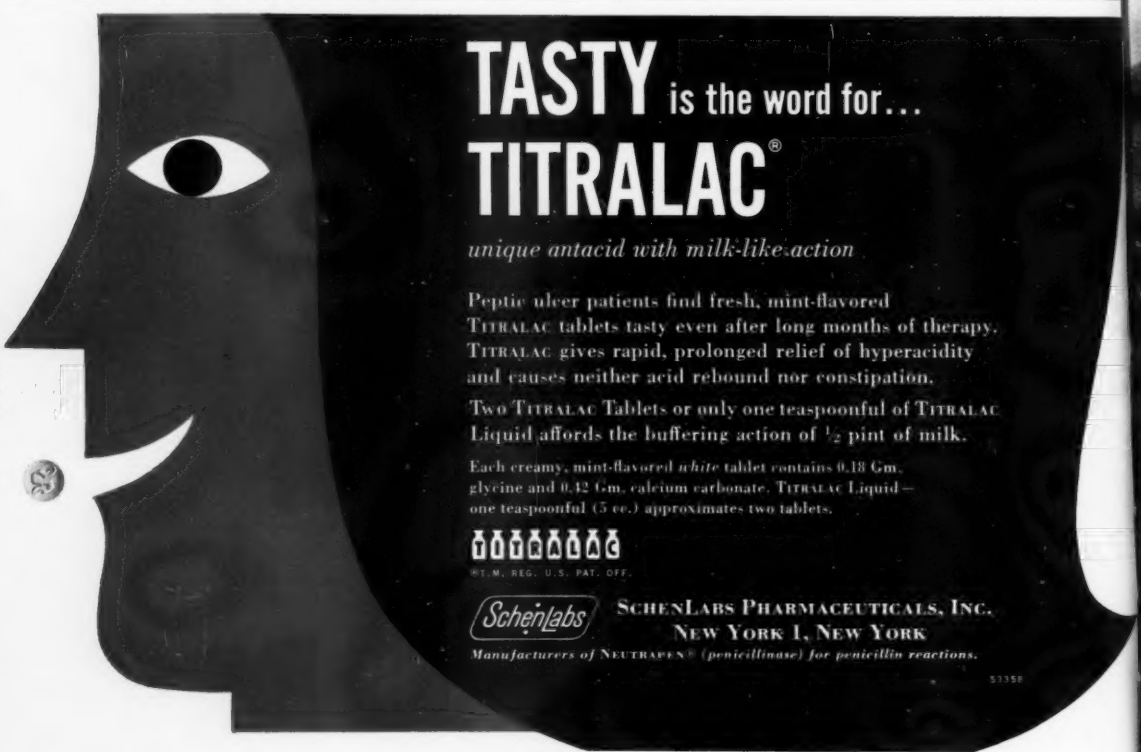
This patient would not be considered sterile, but should be regarded as one whose fertility is reduced. A urologic investigation should be conducted and the necessary treatment instituted to correct prostatitis or any other disorder which might be present in the urinary tract. General hygienic and dietary measures should be reviewed. Occasionally, the administration of a thyroid substance proves beneficial.

• POLIOMYELITIS VACCINE AND PENICILLIN SENSITIVITY

Q. A six year old girl, who has shown sensitivity to penicillin on two occasions, has not been immunized against poliomyelitis because of the small amount of penicillin contained in the vaccine as a preservative. Is it advisable to administer the vaccine to patients who are sensitive to penicillin? Should any precautions be taken other than those for anaphylactic shock? Should the patient be desensitized to penicillin?

M.D.—Manitoba

A. Since poliomyelitis vaccine contains very small amounts of penicillin, the American Academy of Pediatrics has advised: "Use caution in individuals known to be highly sensitive to penicillin or streptomycin." It has been noted that no serious anaphylactic reactions have occurred after several million inoculations and that patients with known sensitivity to penicillin have been immunized without ill effects. The usual precautions against anaphylactic shock should be observed.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Two TITRALAC Tablets or only one teaspoonful of TITRALAC Liquid affords the buffering action of ½ pint of milk.
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THERAPY SHOULD BE INDIVIDUALIZED

acute conditions: Two or three tablets four times daily. After desired response is obtained, gradually reduce daily dosage and then discontinue.

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precautions: Because SIGMAGEN contains prednisone, the same precautions and contraindications observed with this steroid apply also to the use of SIGMAGEN.

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corticoid-salicylate compound tablets

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Acetylsalicylic acid	325 mg.
Aluminum hydroxide	75 mg.
Ascorbic acid	20 mg.

Packaging: SIGMAGEN Tablets, bottles of 100 and 1000.

References: **1.** Spies, T. D., et al.: J.A.M.A. 159:645, 1955. **2.** Spies, T. D., et al.: Postgrad. Med. 17:1, 1955. **3.** Gelli, G., and Della Santa, L.: Minerva Pediat. 7:1456, 1955. **4.** Guerra, F.: Fed. Proc. 12:326, 1953. **5.** Busse, E. A.: Clin. Med. 2:1105, 1955. **6.** Sticker, R. B.: Panel Discussion, Ohio State M. J. 52:1037, 1956.

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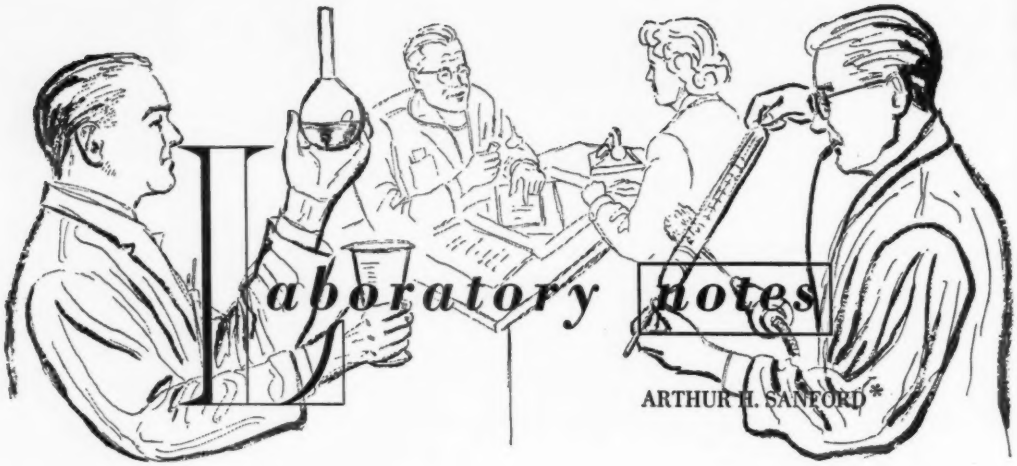
SG-J-618



ARTHUR H. SANFORD*

Hemoglobinometry

RECENTLY a subscriber sent the following inquiry to POSTGRADUATE MEDICINE: "Is there such a thing as a simple, inexpensive, accurate method for determining hemoglobin in the office? If so, would you please let me know what it is."

The answer to the query is, No, but I believe a little more should be said. As many of the readers of this column know, this has been a favorite topic of discussion on my part for a quarter of a century. In fact, in attempting to answer this same question, Dr. Charles Sheard and I devised the first photoelectric colorimeter and made practical a simple, accurate method for determining hemoglobin values. The chief objection to its use is the cost of the PHOTELOMETER®.

It is possible to guess that a patient is anemic by looking at his eyes and the conjunctiva of the lower lids. An experienced clinician may guess within 5 gm. per cent. A slightly more impressive method of guessing is to use a Tallqvist hemoglobin scale. A drop of blood on absorbent paper makes a red stain which is matched against a scale reading in percentages. At the bedside, an experienced clinician can tell if the patient is anemic.

Other direct reading methods such as Dare's hemoglobinometer or the Spencer hemoglobinometer are somewhat expensive and they are not too accurate. By these methods an experienced physician or technologist will probably determine a value within about 20 per cent of the true value, and determinations made separately by two people will usually agree within about 20 per cent of each other. Another inexpensive but not very accurate procedure, well known for years, is the Sahli acid hematin method or one of its modifications. One of the simplest of these is the Haden-Hausser hemoglobinometer. The advantage of using this method is that a dilution of blood for making white blood cell counts, using a decinormal solution of hydrochloric acid, may be used for the hemoglobin determinations. But the brown color is difficult to match to that of the wedge of colored glass; two people will not agree on the results. Clinical experience and comparative results make this a halfway satisfactory method, and it is still probably the most popular method in many office laboratories.

However, hemoglobin is the most important constituent in blood. It is measured in grams per cent—not milligrams, as are so many chemical substances. Does it not deserve an accurate method of determination? The cost of a good photoelectric colorimeter should not

(Continued on page A-30)

*Emeritus Staff, Section of Clinical Pathology, Mayo Clinic; Director of Laboratories, Rochester State Hospital, Rochester, Minnesota.

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be a more important consideration than accuracy and the best interests of the patient, especially if the patient is anemic and is being treated either for iron deficiency or for lack of the antianemic factor. After operation, in conditions of hemoconcentration, sudden drop in blood pressure, and evidence of internal bleeding, a simple but very accurate method of determining hemoglobin should be available in the office laboratory as well as in the hospital laboratory.

While I may be prejudiced in favor of the method that I have used for 25 years for determining oxyhemoglobin, I know of no procedure that is more rapid; a very simple reagent is used in which the blood is laked in a dilution of 1 to 200. There is 25 times as much oxygen in the reagent as is necessary to keep the hemoglobin combined as oxyhemoglobin. The principle in using the Cenco-Sheard-Sanford Photelometer is to measure the amount of light absorption in the green portion of the spectrum, in which is found one of the heavier absorption bands of oxyhemoglobin. There is no visual color matching. The results are repeatable with surprising agreement. In fact, I am constantly surprised at how very repeatable the results are with a photoelectric colorimeter for many chemical determinations. But I believe that hemoglobin determinations may be made that are more in agreement than determinations of many other substances.

The cyanmethemoglobin method recently devised by Dr. D. L. Drabkin is somewhat similar to that in which the Photelometer is used. This is described in two papers.[1,2] In this method, potassium ferricyanide converts hemoglobin to methemoglobin, which combines with potassium cyanide to produce a stable reddish-brown pigment, cyanmethemoglobin. This is measured with a photoelectric colorimeter with a green filter. The reagent is poison.

A manufacturer* of laboratory apparatus has assembled a hemophotometer to be used only for hemoglobin determinations by the Drabkin method. Doubtless this is a very rapid, accurate method. However, the apparatus is not cheap and cannot be used for other chemical determinations. The scale on the meter is calibrated so that all readings are made directly in grams of hemoglobin per 100 ml. of blood.

Again I must answer the inquiry by saying, No, but it is important to use some accurate method.

*Fisher Scientific Co., Pittsburgh.

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1. Crosby, W. H., Munn, J. L. and Furth, F. W.: Standardizing a method for clinical hemoglobinometry. U. S. Armed Forces M. J. 5:693-703, 1954.
2. Crosby, W. H. and Houchin, D.: Preparing standard of cyanmethemoglobin. Blood 12:1132-1136, 1957.

MEETINGS and Postgraduate Courses

American College of Physicians: Postgraduate courses for 1958-1959:

Subjects in internal medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, November 3-7
Gastroenterology, University of Michigan Medical School, Ann Arbor, November 10-14
Congenital heart disease, The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital, Baltimore, November 17-22
Internal medicine—especially therapeutics, University of Illinois College of Medicine, Chicago, January 12-16
Current research in endocrinology, National Institutes of Health, Bethesda, February 2-4
Recent advances in cardiovascular diseases, Mount Sinai Hospital, New York, February 9-13
Recent advances in internal medicine, Pennsylvania Hospital, Philadelphia, February 23-27

For further information, write to: E. R. Loveland, Executive Secretary, 4200 Pine Street, Philadelphia 4.

International College of Surgeons, Miami Beach: Southeastern regional meeting, January 4-7. For further information, write to: Dr. Harold O. Hallstrand, 7210 Red Road, South Miami, Florida.

New York University-Bellevue Medical Center Post-Graduate Medical School, New York: Courses to be presented in 1958-1959:

Ophthalmic plastic surgery (for specialists), November 17-21
Surgery of the cornea, December 1-5
Neuro-ophthalmology, January 19-23

For further information, write to: Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16.

University of Texas M. D. Anderson Hospital and Tumor Institute, Houston: Clinical conference on cancer chemotherapy, in collaboration with the University of Texas Postgraduate School of Medicine, November 14-15. For further information, write to: Dr. C. C. Shullenberger, Department of Medicine, M. D. Anderson Hospital, Houston 25.

What's happening in Medicine

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

COLD VACCINE ONLY A TECHNICAL PROBLEM

Second annual Kansas City Symposium on Infectious Disease:

- Control of mild respiratory diseases, including the common cold, is now only a technical problem. The methods and know-how for the isolation and characterization of new viruses and the production and use of effective vaccines are at hand. Adenovirus vaccines, as used in the Armed Forces and among volunteers, have reduced the incidence of respiratory diseases 80 to 90 per cent. Vaccines consisting of types 3, 4 and 7 have shown such propensity in preventing acute respiratory disease in recruits, the Army is adding them to the list of routine immunizing agents.—Dr. Thomas G. Ward, Lobund Institute, University of Notre Dame, South Bend, Ind.
- Beta hemolytic *Streptococcus* is the offender that must be eradicated to control acute glomerulonephritis. But only under circumstances of mass outbreaks of streptococcal infections with resulting nephritis should widespread antibiotic prophylaxis be undertaken. While acute glomerulonephritis has been shown to follow infections caused by only a few strains of beta streptococci, it may possibly be a sequela to infections by other strains.—Dr. Thomas H. Haight, University of Oklahoma School of Medicine, Oklahoma City.

LIFE SHORTENING BY ROENTGEN RAYS

International Congress of Radiation Research:

- Experiments on mice indicate that fluoroscopic pelvic examination of pregnant women will shorten the life of a fetus about 12 days per roentgen.—Dr. Howard J. Curtis, Brookhaven National Laboratory, New York.
- When administered prophylactically, the synthetic compound **AET** enabled mice to survive twice as much radiation exposure as control animals.—David G. Doherty, Oak Ridge National Laboratory, Oak Ridge, Tenn.

AORTIC SURGICAL MORTALITY REDUCED

Regional Conference, American College of Surgeons, Stockholm:

- Mortality in plastic graft surgery for coarctation of the aorta has been reduced from 7 to 5 per cent in the last two years. About 150 such operations have been performed since 1953 on patients in age groups ranging from children to 83 year old adults. Only plastic prostheses were used.—Dr. Harris B. Shumacker, Jr., Indiana University School of Medicine, Indianapolis.

Chlorpromazine in schizophrenia

Third annual Research Conference on Chemotherapy in Psychiatry:

• Chlorpromazine and promazine are markedly effective in reducing the number and severity of schizophrenic symptoms, as shown in a three month study of 600 Veterans Administration patients in 38 hospitals. Patients are made more responsive, enabling them to participate more actively in rehabilitation activities, group psychotherapy, and in physical medicine and other hospital programs.—Veterans Administration Hospital, Perry Point, Md.

Harmful gene estimate: 4.5 per person

Twenty-fourth semiannual report, Atomic Energy Commission:

• Children of first-cousin marriages were compared with those of control families in an attempt to add to the knowledge of the genetic constitution of man. The frequency of serious illness or death among the consanguineous children was about 12 times that of the controls. Mathematical analysis of this increase and of the very slight increase observed in frequency of miscarriage and stillbirth allows calculation of the probable number of defective genes in both parents. Further calculation permits estimation of the frequency of occurrence of abnormal recessive genes in the common ancestor of these first cousins and provides the best way of estimating the rate of occurrence of recessive genes in modern man. It appears from these studies that people, on the average, carry the equivalent of 4.5 harmful recessive genes.—Dr. E. L. Powers, Argonne National Laboratory, Lemont, Ill.

Herpes virus in multiple sclerosis

National Multiple Sclerosis Society:

• The role of herpes simplex virus in multiple sclerosis deserves investigation. To qualify as a causative agent, the virus (1) would have to be capable of lying dormant in the nervous system and be provoked into repeated bouts of activity, and (2) would have to attack the glia cells regulating the formation of the myelin sheath. It is known that herpes virus has the capacity to multiply in glia cells and can be triggered into action by such physiologic disturbances as allergy, pregnancy or trauma. Recent studies of mice inoculated with minute doses of a strain of herpes virus isolated from a fatal case of human encephalitis revealed that the virus had a marked affinity for glia cells. There was a concomitant destruction of myelin. In two laboratory workers infected with herpes-related "B" virus, as a result of contact with monkeys, demyelinating lesions similar to those seen in multiple sclerosis were observed.—Dr. Albert B. Sabin, Cincinnati.

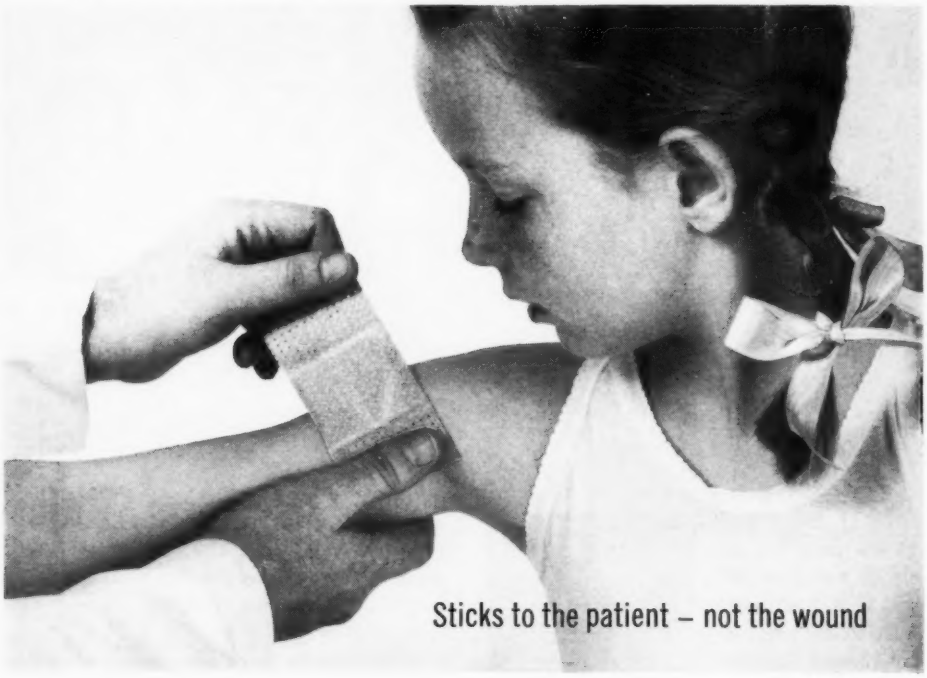
Hypodermic needle contamination

Society of Nuclear Medicine:

• A radioisotope test shows that only 20 per cent of used hypodermic needles are thoroughly cleaned by conventional hospital technics. Eighty per cent remain contaminated by protein which may be injected into another patient. Theoretically, the proteins are capable of setting up an antibody reaction and ultimately an allergic reaction. This may account for unexplained cases of chills and fever among hospital patients. Needles are now used only once at St. Luke's Hospital.—Dr. J. W. Blunt, Jr., St. Luke's Hospital, Cleveland.

• Pain of metastatic bone cancer can be palliated with small doses of oral radiophosphorus. Return of pain is gradual, but the course can be repeated at three month intervals without depressing bone marrow activity.—Dr. William Blahd, Veterans Administration Center, Los Angeles.

HELPING THE HANDS THAT HEAL



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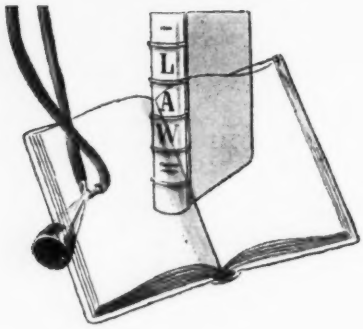

Forensic Medicine

Medicolegal Aspects of Artificial Insemination

JOHN F. LOMBARD*

Suffolk University Law School, Boston

JOHN F. LOMBARD

ARTIFICIAL insemination is not new, but it is only in the past 25 years that it has been practiced to any great extent among human beings. In the fourteenth century the Arabs practiced it among horses,[1,2] and there were later successful experiments with fish[1,3] and dogs[3] and then cows and sheep.[4] Artificial insemination of cattle has been in use for years. Of course, stock breeders are not governed by the social customs, conventions and regulations that the physician dealing with human beings must recognize at all times.[2]

Artificial insemination among human beings reportedly was first successfully accomplished by Eustachius in the middle of the sixteenth century.[1] The English surgeon and anatomist John Hunter described his first successful case of artificial insemination in 1790.[1,4] In the United States, J. Marion Sims reported a case in 1866; he first praised the procedure and later condemned it.[3] In 1936, Francis J. Seymour reported his first case of eugenic practice.[1]

The procedure has been called telegenesis,[5] therapeutic insemination (Dr. R. G. Bunge, *Boston Daily Record*, April 6, 1954), and applied eugenics. The press has referred to babies born as a result of artificial insemination as "test tube babies" (*New York Times*, December 14, 1954; *Boston Traveler*, December 14, 1954). It is a medical procedure under controlled conditions whereby semen is deposited by sterile instrument into the cervical canal. It does not involve personal contact between the persons concerned.

Types of Artificial Insemination

Two types of artificial insemination are generally known and designated. They are homologous insemination or A.I.H.,[6] in which the semen of the husband is used, and donor or heterologous insemination, also called A.I.D.,[6,7] in which the semen of a third person is used. A third type, yet unnamed, involves

(Continued on page A-42)

*Professor of Law, Suffolk University Law School, Boston, Massachusetts.

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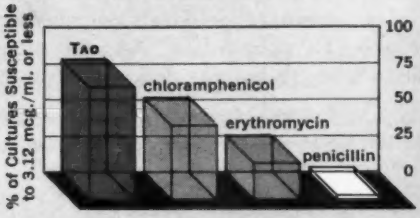
effective . . .

CLINICAL RESULTS	adults	children	all Staph infections
Cured	172 (80%)	148 (89%)	71 (88%)
Improved	28 (13%)	8 (5%)	7 (9%)
Failure	17 (7%)	11 (6%)	3 (3%)

Types of infecting organisms: The majority of identified etiologic microorganisms were Staph. aureus and Staph. albus. Tao has its greatest usefulness against organisms such as: staphylococci (including strains resistant to other antibiotics), streptococci (beta-hemolytic strains, alpha-hemolytic strains and enterococci), pneumococci, gonococci, Hemophilus influenzae.

even against resistant staph[1,2] . . .

Per cent of "antibiotic-resistant" epidemic staphylococci cultures susceptible to Tao, erythromycin, penicillin and chloramphenicol.[1]



well tolerated . . .

REACTIONS:

(a) adults	(b) children
Total—9.2% (20 out of 217)	Total—0.6% (1 out of 167)
Skin rash—1.4% (3 out of 217)	Skin rash—none
Gastrointestinal—7.8% (17 out of 217)	Gastrointestinal—0.6% (1 out of 167)

There was complete freedom from adverse reactions in 94.5% of all patients. Side effects in the other 5.5% were usually mild and seldom required discontinuance of therapy.

[illegible] . . . stability in gastric acid • rapid, high and sustained blood levels • high urinary concentrations • outstanding palatability in a liquid preparation

Dosage and Administration: Dosage varies according to the severity of the infection. For adults, the average dose is 250 mg. q.i.d.; to 500 mg. q.i.d. in more severe infections. For children 8 months to 8 years of age, a daily dose of approximately 30 mg./Kg. body weight in divided doses has been found effective. Since Tao is therapeutically stable in gastric acid, it may be administered at any time, without regard to meals.

Supplied: Tao Capsules—250 mg. and 125 mg.; bottles of 60. Tao for Oral Suspension—1.5 Gm.; 125 mg. per teaspoonful (5 cc.) when reconstituted; unusually palatable cherry flavor; 2 oz. bottle.

References: 1. English, A. R., and Fink, F. C.: Antibiotics & Chemother. (Aug.) 1958. 2. English, A. R., and McBride, T. J.: Antibiotics & Chemother. (Aug.) 1958. 3. Wennersten, J. R.: Antibiotic Med. & Clin. Therapy (Aug.) 1958. 4. Celmer, W. D., et al.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 476.

the pooling of the semen of both the husband and a donor in the hope that it will be the sperm of the husband that will impregnate the wife. I call this type biseminal artificial insemination or B.A.I.

Barren Marriages, Adoption and A.I.H. or A.I.D.

There probably are several million couples throughout the world who are involuntarily childless, and it is reported that there are about two million childless couples in the United States.[8] While many married couples want children and cannot have them for various reasons, strange as it may seem there are others who do not want a child but do have one.* Many fine people seek to adopt a child,† and others resort to artificial insemination either by A.I.H.[9] or by A.I.D.[10] Adoption often satisfies a woman's burning desire for motherhood, and many women who are capable of childbirth seek to adopt a child. Others wish to give birth to a child.

Generally there is a definite reason for use of the semen of a donor other than the husband for artificial insemination. Usually it is because the husband is sterile or has a transmissible hereditary disease[6] such as hemophilia. Normal sexual intercourse may be impossible because of malformation of the penis or the vagina.[6]

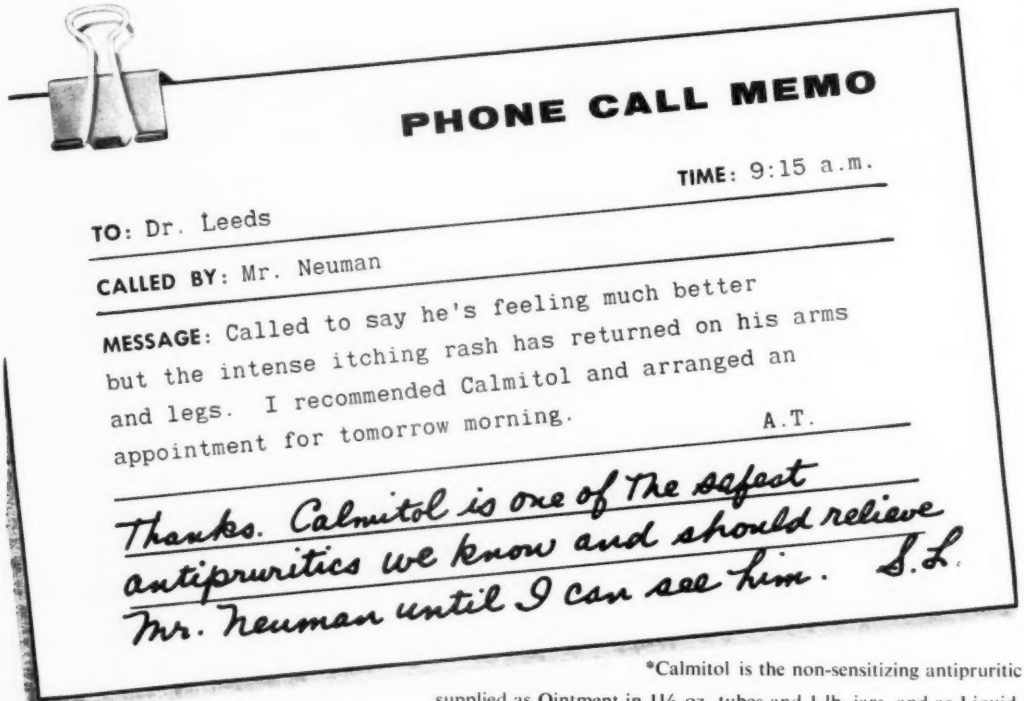
Preparation for Artificial Insemination

Prior to insemination, both the husband and the wife, as well as the donor if one is to be used, are given thorough medical examinations. Various tests are made not only to determine fertility but also to establish the blood types of the persons concerned and detect any evidence of gonorrhea, syphilis or transmissible disease, any of which may make either A.I.H. or A.I.D. inadvisable or impossible. There may be other impediments to concep-

(Continued on page A-44)

*Commonwealth v. White, 329 Massachusetts 51, 106 N.E. 2d. 419; Commonwealth v. Gross, 324 Massachusetts 123, 85 N.E. 2d. 249.

†Gally, Petitioner, 329 Massachusetts 143, 107 N.E. 2d. 21; C.J.S. 2, Adoption, p. 365.


PHONE CALL MEMO
TIME: 9:15 a.m.
TO: Dr. Leeds
CALLED BY: Mr. Neuman
MESSAGE: Called to say he's feeling much better but the intense itching rash has returned on his arms and legs. I recommended Calmitol and arranged an appointment for tomorrow morning.
A.T.
Thanks. Calmitol is one of the safest antipruritics we know and should relieve Mr. Neuman until I can see him.
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Meat functions in several important ways in the dietary management of infectious hepatitis. It supplies large amounts of well-tolerated protein, and it makes meals attractive and appetizing, an inducement to adequate eating in the presence of anorexia.

During the initial stage, when the appetite is especially poor, one of the most acceptable sources of high quality protein is *broiled* ground lean beef. One authority* recommends broiled ground beef three times daily. (Each 3.5 ounces supplies approximately 30 grams of protein.) With the recovery of appetite, other attractively prepared meats also are served.

Meat also helps assure an adequate intake of B vitamins, as well as iron, phosphorus, potassium, and magnesium.

*Kark, R. M.: Nutritional Aspects of Liver Disease in Man, in Wohl, M. G., and Goodhart, R. S.: Modern Nutrition in Health and Disease, Philadelphia, Lea & Febiger, 1955, pp. 597-606.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

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tion on the part of the wife. Sometimes one insemination results in conception, and sometimes several inseminations are required; in other cases insemination is ineffective. It has been reported that a great number of cases of sterility have been cured by means of surgical procedures.[11]

The couple's marriage should be verified, and the physician should be satisfied with their intellectual capacity, emotional stability and the permanence of their marriage.

Selection and Identity of a Donor

Selection of a donor for A.I.D. is vitally important. His identity should be confidential, for social and psychologic reasons, and he should be known only to the physician who performs the insemination (except, as of this date, as set forth herein in the section headed "Legal Status"). A legal problem could arise if the woman knew the donor's identity. Blackmail is a possibility. In Massachusetts, under G.L. (Ter. Ed.) chap. 273, ss. 11-19, and in many other states, if the woman's husband deserted her she might bring a paternity proceeding against the donor. If a court or jury believed that the husband did not consent to the insemination and that the donor was the father of the child, he (the donor) possibly might be adjudicated and have to support the child; and it would make no difference whether such a donor were single or married.[12]

Usually the donor is selected by the physician, and his responsibility in this matter is a great one, as he must comply with rules and regulations from the moral and ethical code of medicine.[13] Donors as a rule are paid various amounts of money for their contribution of semen. No doubt due to the frailty of human nature and the anxiety of husband and wife in A.I.D. cases they generally tell the physician what type of donor they want—tall, light or dark complexion, good physical development, neat, good educational background, and favorable heredity. A donor should never be a relative of either the husband or the wife. The doctor must investigate and select a man in good mental and physical health, if possible one who resembles the husband with regard to physical and emotional qualities.

Care must be exercised in blood grouping and typing.[14] If the wife is Rh-negative, the donor should be Rh-negative. His semen could be used if he were heterozygous, having one positive and one negative gene in reference to the Rh system. This system is also referred to as the CDE system in British nomenclature. Such diligence in blood grouping tends to prevent erythroblastosis fetalis. Alexander Wiener[14] has said that the most common iso-antibody responsible for this disease is a certain Rh factor, and that less commonly it is an Hr factor or an A, B or K factor. Allen and Diamond have described this problem in their recent book titled "Erythroblastosis Fetalis."

Consent of the Parties

Written consent of both husband and wife is given to the physician as a general rule. Some writers have said that if a donor is married his wife should consent to his acting as donor. Personally I cannot see any value of her consent as a matter of law, except that if donor insemination should some day be legally determined to be adultery she might use it as grounds for divorce. In that case, her consent most likely would be a condonation and a bar if a divorce court should consider it in that light (C.J.S. 27, Condonation, sec. 59, p. 608). Consent of the husband to A.I.D. would be a condonation of the process and would bar a libel for divorce by him at a later time. This is true in most states of the United States. A wife might also plead connivance[15] (C.J.S. 27, sec. 64, p. 618) as a defense based on the husband's consent if he should seek a divorce.

There is no definite written form for consent to artificial insemination, so a simple concise writing should be sufficient. Written papers should be kept at a minimum or should not be used at all.

The husband's consent to donor insemination should be voluntary. He should be advised of all facts concerning the procedure as well as what the future may hold after the birth of the child in case of domestic difficulties. Consent of the husband to A.I.D. based on his wife's persuasion because of her desire for a child is really not a solid foundation.

(Continued on page A-46)

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1. Menger, H. C.: J.A.M.A. 159:546 (Oct. 8) 1955.
2. Published and unpublished case reports.

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Adoption of the Child

If it should ever be determined legally that a child born as a result of donor insemination is illegitimate, then the husband may adopt the child and establish a legal status for him. The only problem would be the possible embarrassment in regard to the information required on the adoption petition. Either a husband or a wife or both could execute wills to protect a child born as a result of donor insemination.

Extent of Donor Insemination

Figures on the number of healthy children born and living as a result of donor insemination vary from 3700[16] to 25,000.[8] It has been said that the demand for A.I.D. will eventually reach 10,000 to 20,000 cases per year in the United States.[16] There are no doubt many unpublicized cases. On April 6, 1954, the *Boston Daily Record* carried a report credited to Dr. R. G. Bunge of the University of Iowa that three infants had been born to mothers impregnated with stored frozen semen.

There have been reports of insemination of unmarried women,[16] but society is not ready to accept such practice. It is known that at one time in Germany and in Russia, unmarried women and women separated from their husbands were encouraged to have children for the benefit of the State.[17]

Theological Views

At present, generally speaking, several religious denominations are opposed to heterologous or donor artificial insemination, as it involves the use of a donor other than the husband,[18,19] but are not opposed to homologous insemination, which involves the use of the husband's semen.[20]

The Church of England apparently has sanctioned homologous insemination but not donor insemination. On March 16, 1949, the Lord Archbishop of Canterbury said in the House of Lords: "The practice of artificial insemination by the husband, though it raises certain problems for the moralist, is on the whole justifiable, in that it enables the fulfillment as between husband and wife of one of the chief ends of their marriage and indeed, of Holy Matrimony itself—that is, the procreation of children."[21,22] In short, there is no objection if the semen used is the husband's. The Lord Archbishop said further, "Artificial insemination by a donor is wrong in principle and contrary to Christian standards."[21,22]

On September 28, 1949, Pope Pius XII indicated approval of medical assistance to transfer semen after normal intercourse between husband and wife (*New York Herald-Tribune*, September 30, 1949). At another time, Pope Pius XII said that artificial insemination "outside marriage" is to be considered "absolutely immoral." This condemns donor but not homologous insemination.

In 1877, in a papal encyclical, the Catholic Church condemned the practice as abominable and prohibited it as immoral.[23,24] This was after Mantegazza, a research worker on sexual problems, had for 10 years examined the New Testament and canonical books and literature from a strictly Catholic standpoint and reported that artificial insemination was directly in accordance with the Bible and the book of Genesis. Mantegazza further suggested that assisting the uterus to conceive by artificial means was no more than assisting digestion by means of pills or helping a paralytic foot with the aid of an electric current.[23,24]

In 1939, the Reverend George Kelly,[20] S.J., said that homologous insemination is permissible if the means to accomplish it are not in themselves sinful. His opinion was that donor insemination was not permissible because it allowed a woman to receive into her body the semen of a man not her husband and the husband is not allowed to consent and thereby authorize a violation of the unity of marriage.

In 1947, the Reverend F. J. O'Connell of the Catholic University of America said, in reference to donor insemination (*New York Times*, March 12, 1947): "Since the child so conceived and born springs from parents not married to each other, the procedure is a violation of the social purpose of Matrimony."

It has been said that the Episcopal Church accepts homologous insemination but not donor insemination.[19]

(Continued on page A-48)

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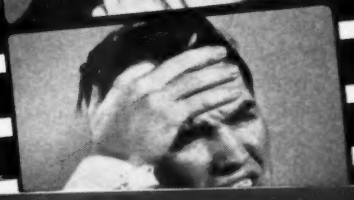
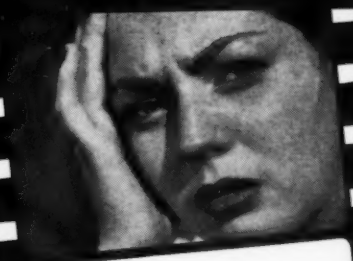
the first concern
in patient
after patient





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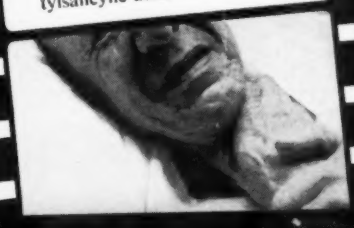

Orthodox Jews hold that Jewish marriages are consummated only by sexual intercourse. As far as can be found, there is not definite acceptance of either homologous or donor insemination. No comment has been found in reference to any definite opinions of the Reform or Conservative groups.[19]

Birth Records

When a child is born as a result of homologous insemination there is no problem in regard to the birth record (G.L., Ter. Ed., chap. 46, sec. 3; Amended Statute 1955, chap. 95, sec. 1). However, birth of an infant after donor insemination does raise problems as to the birth record at the present time. The husband is not the true blood father and there are no statutes clarifying the situation. No doubt in many cases of donor insemination in which the husband consents he is listed as the father in order to avoid publicity and for personal satisfaction.

The laws of all states require the names of the father and mother when a child is born to parents who are married to each other. Listing the husband as the father in A.I.D. cases would violate the statute. Would the husband or the physician or both be subject to fine or jail? If the birth record does not list a father, it would indicate that the child is illegitimate and cause embarrassment when the record is needed for school, etc. An abstract birth record would not indicate illegitimacy.

If a husband dies intestate, a question may arise as to the child's right to inherit. If there is a will or trust creating a right or interest in property in favor of lawful heirs or heirs of the body, it may be necessary to explain the donor insemination birth or face a possible court action by a person who would benefit in the absence of a legitimate heir. When donor insemination births become greater in number and more publicly known, there will be a definite need for legislation to protect children, parents, physicians, hospitals and city and town clerks as well as registers of births and marriages.

Several writers, both in the United States and in England, have suggested that when a wife is pregnant as a result of donor insemination she should be referred to an obstetrician for care and delivery without telling him of the insemination. The obstetrician will then report the birth naming the husband and wife as parents.

Legal Status

The legal status of donor insemination and of the children born as a result of it has not been judicially determined by any of the courts of last resort in the United States to the present time, as far as can be determined. Cases that have reached the courts have concerned divorce,* annulment,† custody,‡ legitimacy‡ and adultery.§ The courts today are in disagreement on the legal status of a child born as a result of donor insemination and are very cautious in their opinions.

The closest approach to an appellate case is Strnad v. Strnad. The sole problem was one of custody and visitation privileges by the husband of a woman who was the mother of a child conceived and born admittedly as a result of donor insemination with the husband's consent. The court allowed visitation to continue weekly. It ruled that since the insemination had been done with the husband's consent the child was not the illegitimate offspring of the wife but was potentially adopted or semiadopted by the husband. The court said it was a situation similar to that of a child born out of wedlock whose parents subsequently married each other and consequently made the child legitimate. The court recognized the legal possibilities in this type of case: "The court does not pass on the legal consequences insofar as property rights are concerned in a case of this character, nor does the court express an opinion on the propriety of procreation by the medium of artificial insemination.

*Doornbos v. Doornbos, Superior Court, Cook County, Illinois, 1954, now reported in 139 N.E. 2d. 844; Hoch v. Hoch, Circuit Court, Cook County, Illinois, 1945. Strnad v. Strnad, 190 New York Misc. 786, 78 New York Supp. 2d. 790.

†R. E. L. v. E. L., 1 Prob. Div. and Adm. 141 (English-1949).

‡Strnad v. Strnad (see footnote above).

§Hoch v. Hoch (see footnote above).

(Continued on page A-50)

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therapy that follows nature's course—TACE, unlike any other estrogen, stores itself in the patient's body fat. Released naturally... slowly, evenly... like a hormonal secretion, TACE provides prompt relief of menopausal symptoms plus sustained symptom-free maintenance because of the unique TACE depot effect.

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With such matters the court is not here concerned; the latter problem particularly is in the fields of sociology, morality and religion."

In Orford v. Orford (49 Ont. Law Reports 15, 1921) there was a libel for divorce by a husband on the grounds of adultery. The wife had spent several years in England, away from her husband, and during a period of proved nonaccess by her husband had given birth to a child. She claimed heterologous insemination and that she had not committed adultery. The Supreme Court, through Justice Orde, said, among other things, that "the essence of the offense of adultery consists, not in the moral turpitude of the act of sexual intercourse but in the voluntary surrender to another person of the reproductive powers of faculties of the guilty person; and any submission of those powers to the service or enjoyment of any person other than the husband or the wife comes within the definition of adultery."

In Hoch v. Hoch, the husband brought a libel for divorce on the ground of adultery based on the artificial insemination of his wife by the semen of a donor. Divorce was denied, and the court said in part, "No definition of adultery includes artificial insemination."

R. E. L. v. E. L.[25] was a libel for nullity of marriage on the ground that the husband was unable or refused to consummate the marriage. It was a psychologic condition with him. Homologous insemination was resorted to from time to time, and not until after the wife left her husband did she discover she was pregnant. The child was born in 1948. Her libel brought thereafter was granted. The court said that her conduct in allowing herself to be inseminated with the semen of her husband did not amount to an approbation of the marriage with an impotent husband and the granting of the decree was not against public policy.

In Doornbos v. Doornbos, the wife was granted divorce but the report does not state the grounds; only an abstract was published. The wife brought libel for divorce and sought sole custody of a son on the ground that he was not the offspring of her husband but was conceived as a result of donor insemination. Judge Gibson E. Gorman held that the husband had no interest in the child and that artificial insemination by a donor not the husband, with or without the husband's consent, is contrary to public policy and the child so conceived is illegitimate. The court further said that if the husband is the donor for artificial insemination the practice does not violate public policy or morals.

The New York City Department of Health took cognizance of the medicolegal aspects of artificial insemination with a donor's semen by amending its sanitary code (section 112) on July 1, 1947, and November 9, 1950. Briefly the amendment regulates the providing of seminal fluid for artificial insemination and requires the physician to keep records of the names of all parties; it requires a complete physical examination for venereal disease, tuberculosis and transmissible hereditary diseases; if a recipient is Rh-negative the donor must be Rh-negative. The records are confidential and only opened to inspection by the Commissioner of Health or a person authorized by law to examine them.

There is no doubt as a matter of law that a child born as a result of homologous insemination is legitimate.* As far back as 1908,[26] German decision recognized that artificial insemination between husband and wife is a legitimate procedure and cohabitation of the parties is not a prerequisite of the legitimacy of the child. In cases of donor insemination there is at present the legal question of whether the child is legitimate or illegitimate, and there are also the problems of custody rights, support, domicile, inheritance, necessary consent to an adoption, and others. Would the highest appellate court of the state hold donor insemination to be adultery? If so, it would be a ground for divorce in most states (C.J.S. 27, Divorce, sec. 21, p. 541). Statutes and decisions of supreme courts clearly indicate that adultery implies a physical sexual relationship between a male and a female.†

*Sayles v. Sayles, 323 Massachusetts 66, 80 N.E. 2d. 21; Silk v. Silk, 325 Massachusetts 487, 91 N.E. 2d. 200.

†Hayden v. Hayden, 326 Massachusetts 587, 96 N.E. 2d. 136; C.J.S. 2, Adultery, sec. 1, p. 472; Black's Law Dictionary, ed. 4, p. 71.

(Continued on page A-52)

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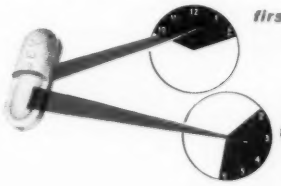

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In donor insemination there is no such relationship; it is an asexual clinical process, without lust, passion or carnal knowledge as the parties never see each other.

It is recognized in all states that a child born in lawful wedlock is presumed to be legitimate. This is a strong presumption but it can be rebutted by evidence which proves beyond a reasonable doubt that the husband could not be the father, as in the case of nonaccess, impotence or clear exclusion by blood test.* When the semen of the husband and that of a donor are pooled for insemination it would be difficult to prove beyond a reasonable doubt that the husband is not the father of the child.

A child born in lawful wedlock as a result of homologous insemination is presumed, according to the interpretation of the law, to be legitimate because he or she was born while the parents were married to each other. There is no problem in cases of homologous insemination. The question that disturbs writers and judges seems to be the legal status of a child conceived and born in lawful wedlock as a result of donor insemination with the consent of the husband. Legislation declaring such offspring to be the legitimate child of the husband and wife is a direct solution.

It is well known that the law follows rather than precedes various scientific advancements and social customs. It is equally well known that science and custom are the basis for much legislation. In view of the advances in human artificial insemination, there are bound to be laws enacted on the subject in the near future.

Legislation

As far as can be ascertained, none of the states in the United States have laws on homologous insemination or donor insemination except for the New York Sanitary Code already mentioned. The following states have introduced bills but none of them have been enacted: Virginia, Senate Bill 199 (1948); Wisconsin, Assembly Bill 407A (1949); Indiana, House Bill 350 (1949); New York, Senate Bill 587 (1950); Minnesota.[27]

*Commonwealth v. Kitchen, 299 Massachusetts 7, 11 N.E. 2d. 482; Sayles v. Sayles; Commonwealth v. Stappen, 1957 Massachusetts Adv. S.H., 815, 143 N.E. 2d. 221 (blood group exclusion).

Summary

The subject of artificial insemination brings to light questions and problems in sociology, morality, religion, mental and physical health, blood grouping and typing, and possibly in some circumstances psychiatry.

Research indicates that at present there are no statutes in the various states either for or against artificial insemination, either homologous or donor, except the amendment of the New York Sanitary Code which regulates the providing of seminal fluid and requires a record of the names of the parties concerned, complete physical examination for venereal disease, tuberculosis and transmissible hereditary diseases, and the selection of Rh-negative donors for Rh-negative recipients. Records are confidential and open only to the Commissioner of Health or other legally authorized persons.

In short, no laws have been enacted making it a crime for any of the parties concerned to take part in artificial insemination. It would seem, in the absence of law prohibiting it, that artificial insemination is a decision of conscience that must be made by the parties concerned. The general practitioner or the specialist must determine above and beyond the parties concerned whether he desires to act in these matters.

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(Continued on page A-54)

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Radiology FOR PRACTICING PHYSICIANS

Duodenal Ulcer

PAUL C. HODGES*

THE shrewd analysis of a carefully taken history usually will suffice for the diagnosis of peptic ulcer; however, except for the fact that the distress tends to localize in the right side of the epigastrium in duodenal ulcer and in the left side in gastric ulcer, the history will not differentiate between the two, and radiologic examination is required.

Palmer[1] has described the clinical findings that lead to the diagnosis of peptic ulcer. The ulcer distress usually is described as gnawing, aching or, sometimes, burning or similar to hunger, except that it is steady and continues for an hour or more in the absence of treatment. Distress usually does not appear until from one to four hours following breakfast and then continues until relieved by the noon meal. It recurs from one to four hours after that meal, usually being more severe than in the morning and usually continuing unless relieved by food, alkali, vomiting or rest. If pain recurs from one to four hours after supper, it usually is less severe than in the afternoon; if it does recur and is relieved by food, etc., it may occur again during the night.

It is commonplace for ulcer patients to acquire the cathartic habit, and the symptoms of this may obscure ulcer distress. Usually, however, the skillful, diligent questioner will be able to bring out a typical ulcer history, even though at first questioning the history seemed to be atypical. If in addition to a typical history an analysis of the gastric juice shows a 12 hour production of acid from 1000 to as much as 6000 or 7000 mg. (average for duodenal ulcer, 2200 mg.; average for normal subject, 660 mg.), almost certainly a peptic ulcer is present, but it still remains to be determined whether it is in the stomach or in the duodenum.

X-ray Findings in Duodenal Ulcer

In more than half of the patients submitting to x-ray examination of the upper alimentary tract, the normal duodenal bulb fills readily with the barium mixture and retains it long enough for adequate filming; sometimes the filled phase is very brief, and occasionally

*Emeritus Professor and Chairman, Department of Radiology, University of Chicago, Chicago, Illinois.

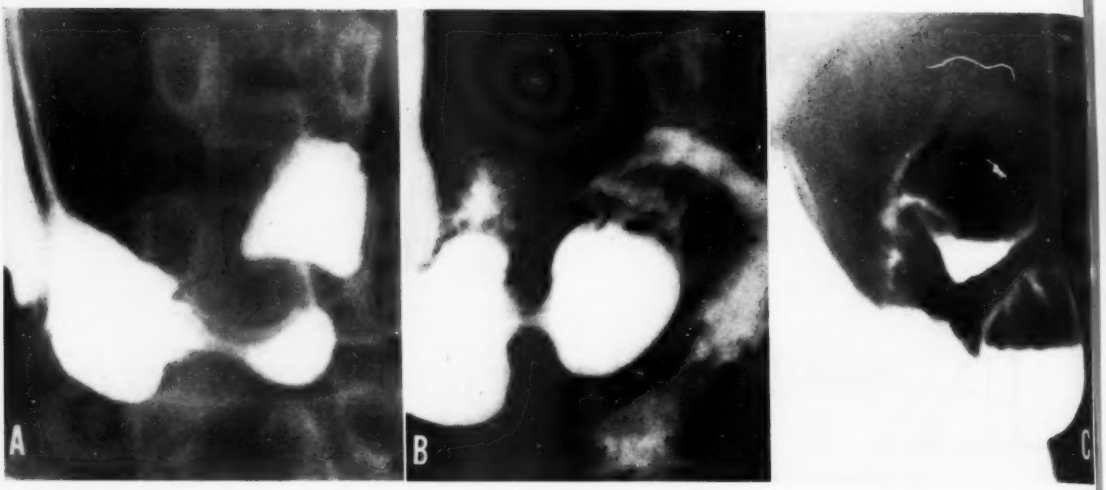


FIGURE 1.

there is no differentiation at all between the bulb and second portion of the duodenum. In a typical normal person (figure 1A), the distal surface of the pyloric muscle produces a clear-cut horizontal base to the bulb, and the downward turn where the superior and descending portions of the duodenum meet forms a sharply rounded apex. The long axis from base to apex may parallel the spine or be angled toward or away from it, and the bulb may lie either beneath the ribs where it is inaccessible to palpation or well down in the abdomen where palpation is easy. In the erect patient, usually the best view is obtained in first oblique position (his right shoulder rotated toward the examiner); but sometimes the reversed or second oblique position is better, and occasionally the bulb is thrown free from neighboring structures only in the full lateral position.

For many years the x-ray diagnosis of duodenal ulcer rested on the demonstration of deformity, "irritability" and obstruction. Since the publications of such workers as the late Åkerlund,[2,3] the direct visualization of the crater has become the principal aim of the examiner. In a severely deformed bulb, peripheral scar pockets may simulate craters, particularly to the inexperienced examiner; on the other hand, a frank crater in an undeformed bulb may escape detection if compression is not employed. The mere failure to be able to obtain films of the filled bulb no longer is interpreted as evidence of ulcer deformity; one requires that deformity of a characteristic type be seen. Deformity produced by severe obstruction is obvious to the radiologist, but judgments as to the degree of incomplete obstruction should be rendered and accepted cautiously.

Duodenal Ulcer With Crater in Deformed Bulb

The case illustrated in figure 2 is that of a 32 year old man. With the patient in the left anterior oblique position (figure 2A), an enormous ulcer crater is seen projecting from the posterior wall of the seemingly undeformed bulb. When he is turned into the right anterior oblique position and pressure is applied (figure 2B), the crater is seen *en face*, with moderate deformity of the bulb about it. Three years later (figure 2C), the compressed bulb demonstrates only residual ulcer deformity at the apex.

Ulcer Deformity of Bulb

Some ulcer craters heal without demonstrable residual deformity, but in most cases they leave a puckered scar which may be so pronounced as to be visible in all phases of filling but more commonly is seen best in compression views. When deformity is of maximum grade, three or more scar pockets may form at

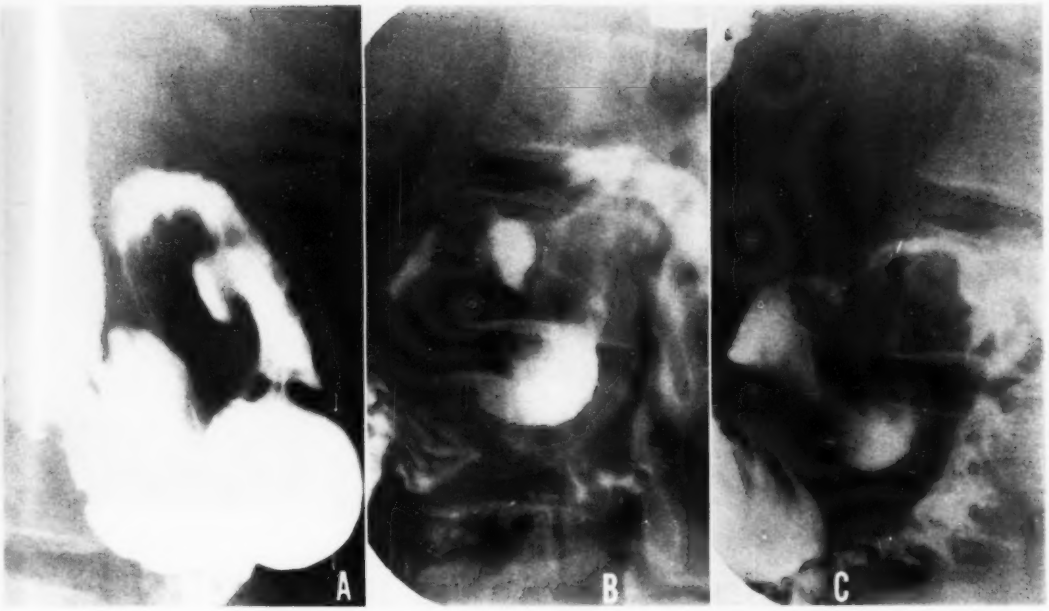
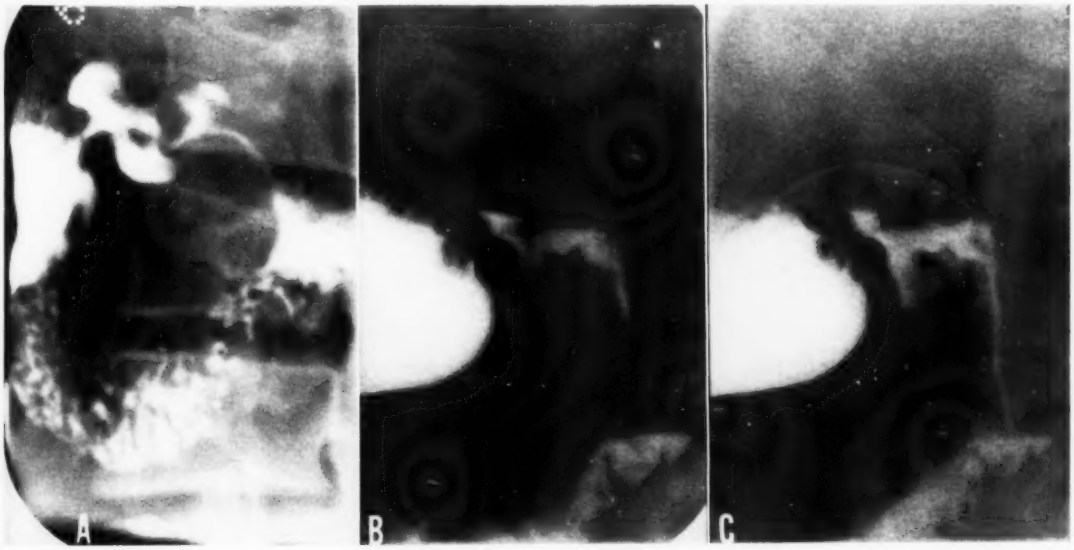


FIGURE 2.

the greater and lesser curvature sides of the base, at the apex, and elsewhere; and in such cases it may be difficult to render judgment as to whether one or more craters may be present as well. Figure 3A shows a central crater in the deformed bulb of a 34 year old man; figure 3B and C shows the persistence of deformity but disappearance of the crater six

FIGURE 3.



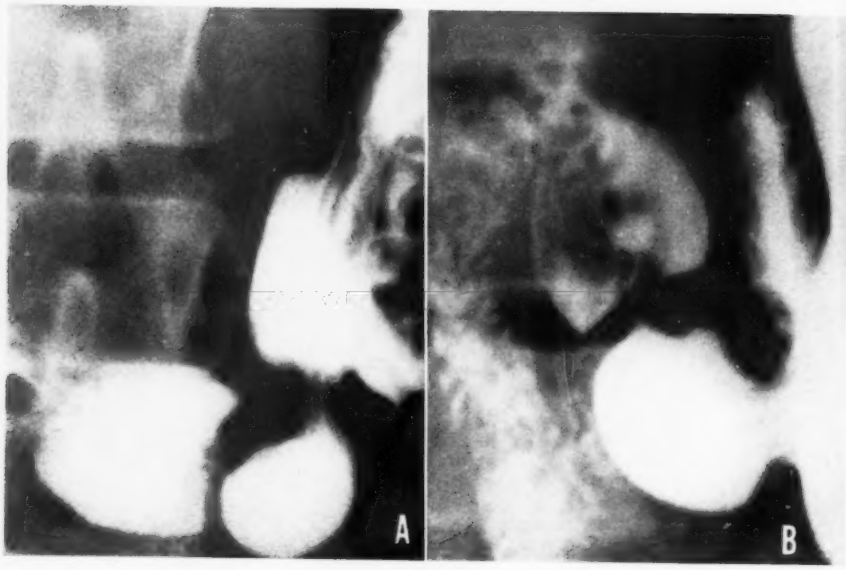


FIGURE 4.

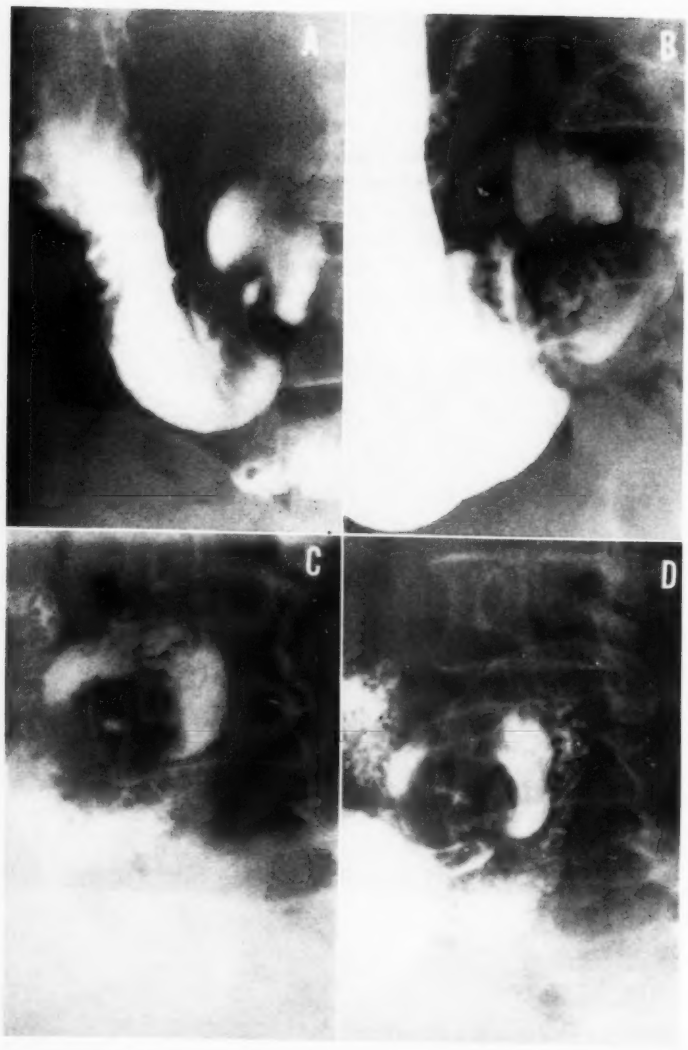


FIGURE 5.

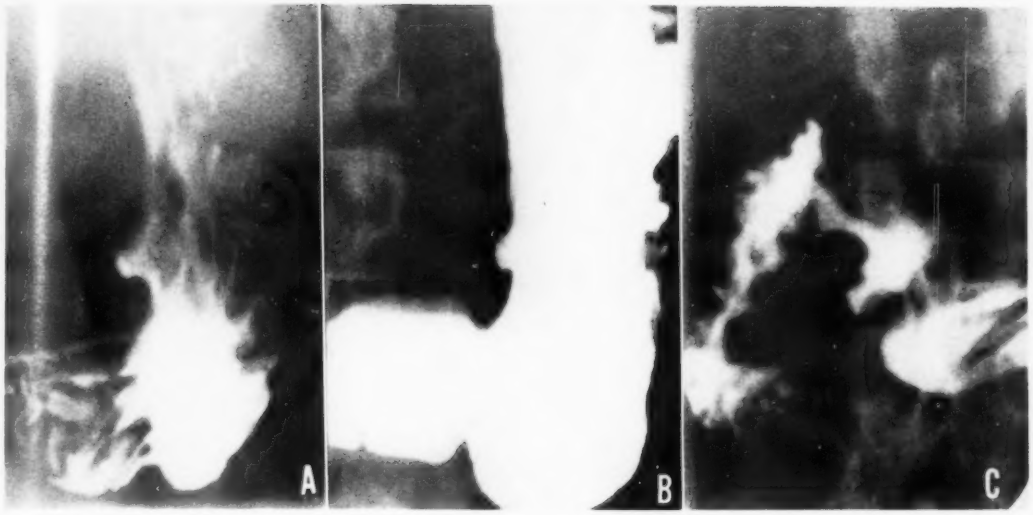


FIGURE 6.

months after vagotomy. At no time was obstruction seen.

Ulcer Crater in Undeformed Duodenal Bulb

When the bulb is undeformed, an ulcer crater is easily overlooked unless compression is employed. In the case illustrated in figure 4, a 39 year old woman had had typical ulcer symptoms for three years. The bulb was completely without deformity (figure 4A), and it was only when compression was applied that the central 1 cm. ulcer crater was demonstrated (figure 4B).

Pyloric Star

Sometimes when an ulcer crater lies in the center of the base of the duodenal bulb very close to the pyloric canal, it may be confused with the so-called pyloric star, which is a fleck of barium that in some patients remains in the normal pyloric canal after the muscle has closed. Figure 5C shows such a pyloric star in a 68 year old woman in whom there was no clinical reason to suspect duodenal ulcer; the appearance had not changed five months later (figure 5D). In another case, however, the central fleck seen at the base of the bulb in figure 5A was interpreted as a crater rather than a pyloric star. Three months later, following management and the subsidence of symptoms, the fleck had disappeared (figure 5B).

Coincidence of Gastric and Duodenal Ulcer

Infrequently the two lesions are seen in the same patient. In the case illustrated in figure 6, a 46 year old man had an 8 by 8 mm. gastric ulcer protruding from the lesser curvature of the body of the stomach just proximal to the incisura angularis and, in addition, a typical residual ulcer deformity of the duodenal bulb without crater or obstruction. Following four months of medical management, the gastric ulcer had healed without leaving a deformity, but deformity of the duodenal bulb was unchanged. No special diagnostic problems are involved in such cases if one avoids the tendency to be satisfied with the finding of one lesion without looking carefully for a second.

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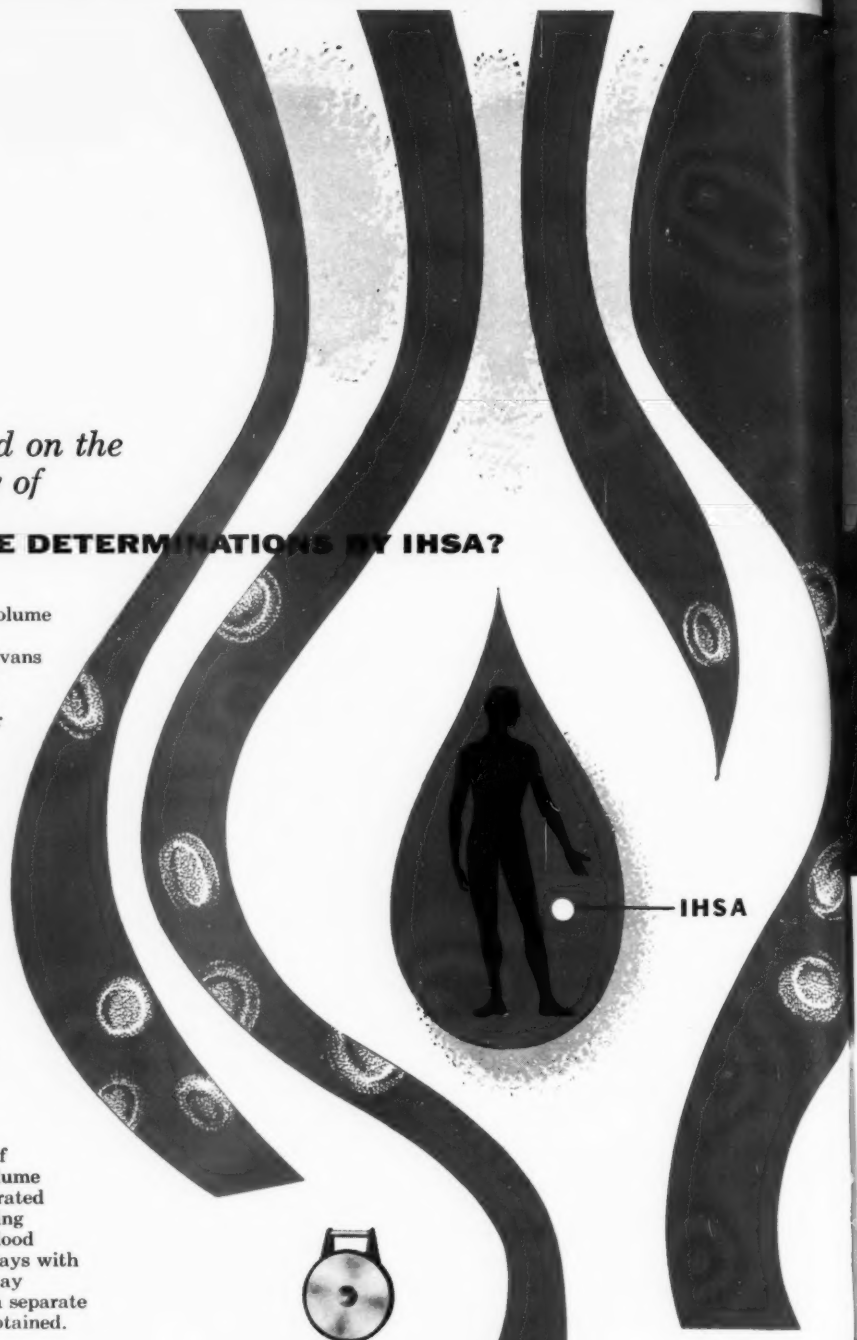

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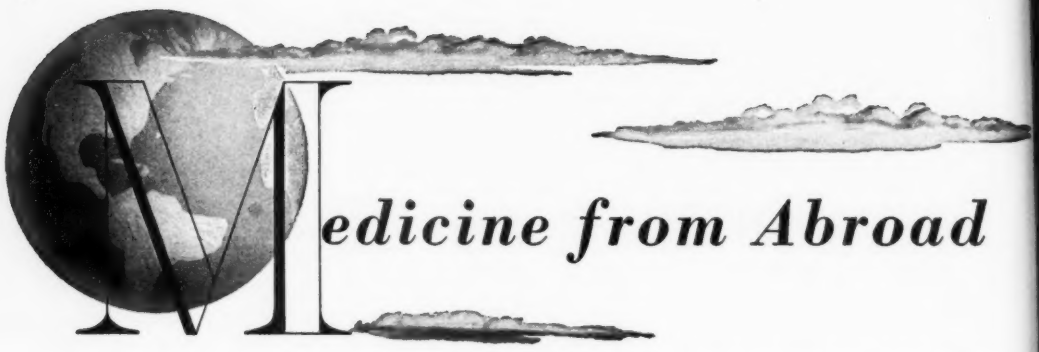

Medicine from Abroad

FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS

AUSTRALIA

Lead poisoning and chronic nephritis— In the *Australian Medical Journal* Dr. D. A. Henderson has related a fascinating story of preventive medicine evolving from the custom in Queensland of building houses high above the ground for coolness and of painting the timber studs with lead paint.

The first mention in the literature of a particular problem in relation to chronic nephritis in Queensland was in 1897. Halford, in discussing lead poisoning in children, observed that granular contracted kidneys in persons less than 30 years of age were found more frequently in Brisbane than in the southern cities of Australia.

In a 1922 historical account of lead poisoning in Queensland children, the Council to the Queensland Branch of the British Medical Association stated that some Brisbane practitioners strongly believed that the prevalence of chronic nephritis among young adults in the city was partly a late result of the absorption of lead during childhood. Chronic nephritis was unduly prevalent among young people in Queensland, and at that time about 90 people less than 30 years of age and approximately the same number between the ages of 30 and 50 years died annually of the disease. This was in excess of the number of people who would have died of the disease if the death rates were the same as those of England and Wales.

The evidence suggested that lead poisoning during childhood was a major factor in causing the abnormal incidence of chronic nephritis in Queensland. Although it appeared to be the sole factor, according to the account, it could not be stated definitely that such was the case.

No further inquiries were made until investigations were begun in 1951. On the basis of mortality data between 1876 and 1947, the excess mortality from chronic nephritis in Queensland is best explained by the action of a nephrotoxic agent on the children. Such an agent would have become active about 1880, initiating changes in the kidney leading to death from chronic renal disease 10 to 40 years later; it gradually became inactive after 1920.

According to manufacturers, the other constituents of the lead paint used in Queensland before 1920 were linseed oil and a very small proportion of driers, which were metallic salts having a catalytic action. In the course of drying, polymerization of the linseed oil occurred, with the production of insoluble and inert resins. The same substances were used in the zinc paint which replaced lead on surfaces accessible to children. A subsequent decline in plumbism and mortality from chronic nephritis was noted.

If lead nephrosclerosis has occurred to any degree outside Queensland, Henderson concluded that it probably has been diagnosed in the past as hypertensive nephrosclerosis or as chronic

(Continued on page A-86)

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pyelonephritis, while a smaller number of cases may have been called chronic glomerulonephritis or gout.

Bornholm disease—An outbreak of Bornholm disease in a circumscribed area in an Adelaide suburb was studied and discussed by L. Kaupmees and R. A. A. Pellew. The disease showed one or two unusual clinical and epidemiologic features.

In the series of 23 patients the outstanding symptoms were as follows: (1) An intense headache of insidious onset and usually of a bursting nature, occipital or frontal, or both, remained constant for five days or more. (2) A low grade fever, the temperature rising to 100° F. in the evening, usually lasted five to seven days. Of interest was the sustained fever in five cases in which there was a persistent elevation of temperature from 99 to 99.8° F. for as long as six weeks; in fact, in one case such fever persisted for three months. (3) All patients complained of stiffness of the neck accompanied by much muscular pain. (4) Muscle pain was consistently experienced along both sides of the attachment of the diaphragm, more anteriorly than posteriorly. Other sites of pain were the upper part of the trapezium and, peculiarly, a triangular area in the quadriceps femoris in the front of the thigh. All patients complained of pain in the orbit when moving their eyes from side to side. The authors believed this to arise from the extrinsic eye muscles. There was much less consistent pain in other parts of the body, such as the upper part of the arm and the calf. (5) Nausea, vomiting and constipation were common and vertigo occurred in every case.

There were no notable physical signs except tenderness under both costal margins and neck stiffness. A pleural friction rub was not discovered in any case. In a few patients, the severe upper abdominal pain and tenderness simulated an acute condition within the abdomen, but the pain on eye movement, headache, and pain in the front of the thigh were sufficient to exclude this diagnosis. The authors considered these symptoms sufficient to warrant a diagnosis of Bornholm disease.

The therapy consisted of bed rest and treatment of the symptoms. Patients obtained marked relief from the unpleasant vertigo when given DRAMAMINE® derivatives which were combined with pyridoxine. Patients with sustained pyrexia presented a greater problem. It is very difficult to continue to reassure a depressed patient who sustains an elevated temperature in the evening. Combating this problem of continued fever in a disease resembling poliomyelitis, one of the authors achieved good results in several cases by using intravenous injections of arsenic.

The significance of the constant headache, which in most cases was not overshadowed by the chest pain, was stressed. The pain in the front of the thigh was real. The sustained fever (also recorded in an Oxford epidemic) and the ensuing psychologic symptoms were emphasized.

The failure to isolate viruses and to demonstrate rising antibody titers was discussed; however, in spite of this, it is believed possible that the outbreak may be attributed to the Coxsackie B2 virus.

AUSTRIA

Latent genital tuberculosis in women—Addressing the Austrian Society for Gynecology and Obstetrics regarding latent genital tuberculosis in women, Dr. J. Halbrecht of Israel discussed (1) the importance and likelihood of an early diagnosis, (2) results of antibiotic therapy, and (3) spontaneous cures and their consequences. The culture of menstrual and intermenstrual excretions and the stroke curettage are reliable diagnostic procedures; but the results of hysterosalpingography are more questionable. Culture of the menstrual excretions seems to be the most accurate method, since it is not possible to detect the first (tubal) stage of genital tuberculosis by means of stroke curettage. However, these methods supplement each other. Halbrecht diagnosed 89.2 per cent of cases by cultures of the menstrual blood and the remainder by stroke curettage.

Discussing the use of chemical and antibiotic remedies, Halbrecht stated he obtained the most favorable results by using a combination of streptomycin-PAS and isoniazid. Eighty per cent of patients with genital tuberculosis appeared to be treated successfully in this way, but a definite cure cannot be accepted until a four year follow-up observation reveals no recurrence. Twenty-three patients (18 per cent) became pregnant after antibiotic therapy; of these, 17 had an extrauterine pregnancy, three aborted, and three had a normal delivery. None of the patients with cured tuberculosis of the endometrium had a full-term pregnancy. The three patients who had nor-

(Continued on page A-88)

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mal deliveries had tuberculosis of the fallopian tubes which could be completely cured.

Spontaneous healing seemingly occurred in at least eight patients, although there are no reliable criteria for definitely establishing the cessation of a tuberculous process in the female genitalia. The prevention of genital tuberculosis is important, since even a spontaneous cure has a destructive effect on the vital functions of the genitalia.

In conclusion, Halbrecht stated that he does not agree with his American colleagues that genital tuberculosis is a problem only in economically and socially backward countries. Statistics show that an equal percentage of genital tuberculosis is found in cases of sterility in such countries as Sweden, England, France and Israel.

Dr. H. Knaus remarked that Halbrecht's observations and experiences, especially referring to the initial infection of the tubes, the descending characteristics of the disease, and the frequency of sterility, agreed with his own findings. However, he seemed more frequently to have encountered severe forms of genital tuberculosis which could be quickly and permanently cured only by surgical intervention. Only the more seriously affected tube is removed, and since the uterus and ovaries are retained the reproductive function of the genital organs is preserved. The tubal changes in nearly all patients on whom Knaus operated were such that the primary or secondary sterility could not have been corrected by conservative therapy.

Dr. J. Froewis stated he believed genital tuberculosis could be treated successfully by conservative means and suggested using massive inoculations of Old tuberculin. However, radical surgery is necessary if conservative therapy fails or if more extensive tumors are present. Froewis was surprised by the high percentage of positive cultures of menstrual blood obtained by Dr. Halbrecht since he, like the majority of authors, could obtain only a little over 60 per cent. He reiterated his belief that at the stage at which it can be detected genital tuberculosis should be considered a generalized form of tuberculosis of the whole organism. He believes that hematogenic spread of the disease, conditioned by vascular anatomy, occurs in the mesenchyma of the tubes and the uterine mucosa at the same time. Statistics show that the tubes were affected in 100 per cent and the uterus in at least 90 per cent of patients examined at autopsy. In 20 to 80 per cent of the patients, tuberculosis was present in tissues that are less susceptible to the spread of infection.

Froewis further confirmed the value of conservative therapy by pointing out that four patients with certified and treated tuberculosis became pregnant. Two of the pregnancies were in patients with tuberculous endometritis; abortion occurred in one patient who was not cured. A woman with peritoneal genital tuberculosis who was cured with inoculations and underwent a sterilizing operation has given birth to one healthy child and is expecting a second child.

Dr. J. Spurny discussed the effectiveness of the Froewis method of large-surface inoculations of Old tuberculin in an 18 year old girl. The patient, who had infrequent and irregular menstrual periods for a year and contact bleeding for a shorter time, was admitted to the clinic with the diagnosis of cervical carcinoma. Histologic findings at curettage showed caseous tuberculosis of the vaginal cervix. After 13 inoculations of Old tuberculin, she was clinically cured.

BRAZIL

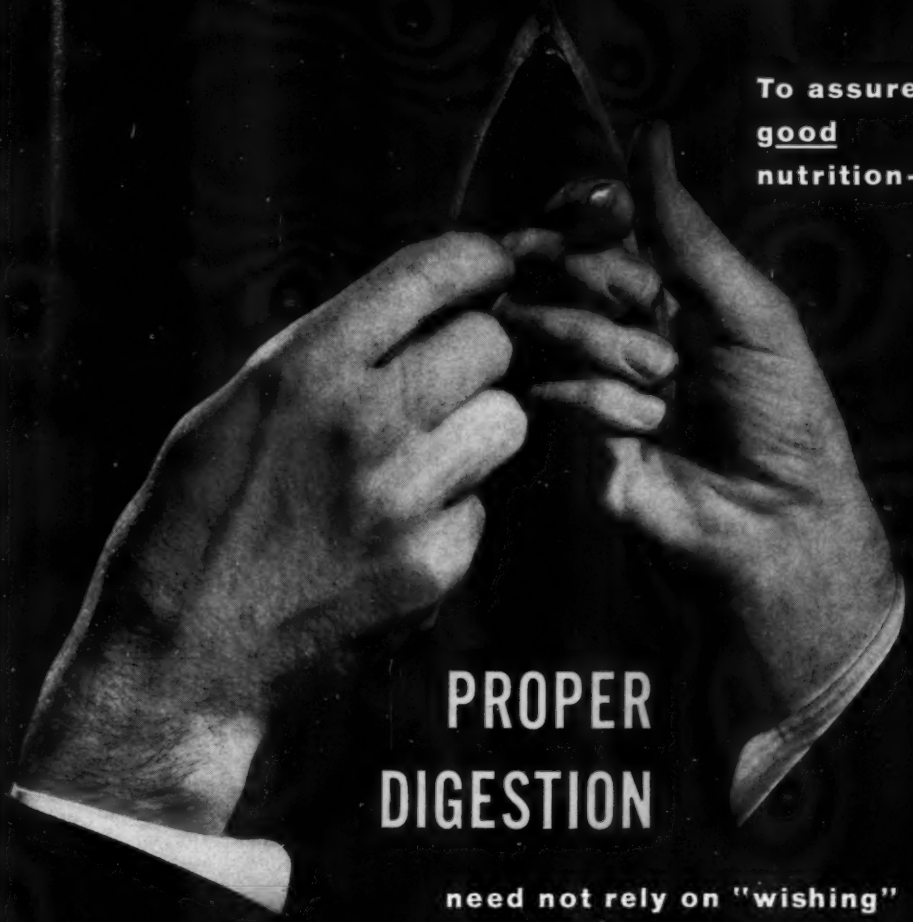
Intra-arterial oxygen—In *Revista paulista de medicina*, Dr. Francisco Luiz Cardamone recently reported that 26 intra-arterial injections of oxygen were given to 15 patients with arteriosclerosis or thromboangiitis obliterans. Analyses of the thermometric and oscillometric variations showed that therapeutic results were relatively good in patients who had no signs of ulceration and gangrene.

In the author's opinion the response to and results from intra-arterial oxygen were not related to sympathetic innervation. In cases in which sympathectomy resulted in partial improvement, administration of intra-arterial oxygen proved beneficial.

Surgical treatment of mega-esophagus—The conclusion drawn from a critical analysis of the treatment of mega-esophagus made by Drs. L. H. Camara Lopes and Ruy Ferreira Santos of the surgical department of the medical school of Ribeirão Prêto also was published in *Revista paulista de medicina*.

From their experience, the authors consider operation the treatment of choice in mega-esophagus. However, they disagree with those who advise only one type of operative management for this disease, for it has several phases of exten-

(Continued on page A-90)



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sion and severity. Although dysphagia is a chief symptom, it may not be the only one. Experience has shown that primary, secondary or associated lesions may occur in the whole organism and thus also deserve consideration.

According to clinicoroentgenographic data, three degrees of severity may be observed in mega-esophagus: (1) slight dysphagia, roentgenographically determined moderate enlargement (4 cm. in diameter), and, in many cases, continued normal contractility; (2) a long history, increased dysphagia, regurgitation, sialorrhea, hypertrophy of the parotid gland, loss of weight, and x-ray findings of 4 to 7 cm. diametric enlargement and stagnating contents filling the esophagus; and (3) increased severity of same symptoms. Sometimes there is no dysphagia, but pulmonary complications due to nocturnal regurgitation. X-ray examination shows an atonic, elongated, sinuous esophagus (more than 7 cm. in diameter) invading the right side of the pulmonary area over the right side of the diaphragm.

Heller's operation is indicated for the first degree of the condition, unless a previous endoscopic examination has shown signs of fibrosis. Infra-aortic partial esophagectomy should be done in cases of the second degree, and subtotal esophagectomy followed by a retrosternal esophagogastric anastomosis performed for the third degree. In 40 operations done for mega-esophagus at the medical school of Ribeirão Prêto, only one patient died from mediastinitis due to intraoperative contamination.

Reoperation of the biliary tract—In presenting the results of their study on the causes for reoperating on the biliary tract, Drs. David Rosenberg and Fernando de Camargo Viana concluded that the best way to avoid the remaining stones and traumatic lesions of the common duct is to obtain a good operative field. Based on their experience of using a right-sided thoracico-abdominal approach in 21 operations of the biliary tract and pancreas, the authors advocate this incision in reoperation of the biliary tract and when some difficulty is foreseen, as in the case of obese patients and in the presence of acute cholecystitis.

Hospital Albert Einstein—A new hospital is planned by the 60,000 Jewish people of São Paulo. Designed by the well-known architect Rino Levi, the hospital will include all the developments of modern medical science and will be open to people of all religions and races.

ENGLAND

Ten years of the National Health Service—In commemoration of the tenth anniversary of the National Health Service, *The Times* published an elaborate supplement and the *British Medical Journal* issued a special supplement of eight articles by a varied selection of authors, along with pungent editorial comment and photographs of the seven ministers of health who presided over the service in the past 10 years (including those who held office only a few months). In addition, a polite editorial on "partnership" appeared in the *Lancet*. These publications conveyed a general impression of national and medical complacency. Britain seems rather smugly to pride herself on a universal health service unequaled in the world. As *The Times*' opening article put it, "Conceived by a Liberal, nurtured by a coalition government under a Conservative prime minister, and brought to life by a Labor Government, the National Health Service can justly claim to be a national institution."

Is this attitude justified? Is "socialized medicine" then a success—at least in England? It must be remembered that the present program was not the result of a sudden new growth. It dates, not from the Socialist experiment of 1946, but from Lloyd George and his National Insurance Act of 1912 and, before that, from the old "clubs" in industrial districts. Although criticism may be directed against the National Health Service, at least it is more comprehensive than the national insurance scheme and more ethical than the old "club" doctoring. However, most of the advances popularly put down to the National Health Service can be credited more correctly to the advances of modern medicine.

The average family doctor in England is usually critical of the National Health Service, although he seems glad enough to take part in it and rather vaguely in favor of its reform. He receives little help from the attitude of the British Medical Association. A few years ago, the Danckwerts arbitration award went to the head of the B.M.A.; instead of an expected award of about £3 million at most (less than $10 million) the family doctors were awarded over £40 million (over $120 million) in increased remuneration

(Continued on page A-92)

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and back pay. The general policy of the B.M.A. today toward the National Health Service appears to be that what is unethical and unacceptable becomes at once ethical and acceptable if there is a bit more money in it.

It is true that there has been a more even distribution of well-qualified specialists throughout the country, and the family doctor in any location is able to bring a consulting surgeon or physician to the bedside of a sick patient in the humblest cottage without any financial obstacle or deterrent. However, the hospitals—even the most famous, such as St. Bartholomew's or St. Thomas's—are out of date and urgently need replanning and rebuilding; but there is no hope for this in the foreseeable future. There are few hospitals (and those of inferior status) to which the family doctor has easy access, and he encounters difficulties when he needs x-ray or pathologic facilities. On the other hand, the average competent family doctor is so busy that he is not prepared to give a half day once or twice a week to working in his local hospital. In his article in the *British Medical Journal*, Dr. Guy Dain, former chairman of the Council of the B.M.A., seemed to advocate a charge for late and night calls—forgetting that the main political basis of the National Health Service is that access to all medical services should be free at the time needed.

The development of the National Health Service in England has been gradual and patchwork, and it is not "designed for export." It is an essential part of the modern welfare state, which in England is accepted—indeed, welcomed—as much by the Conservatives as by the Socialists. It is probably not a coincidence that communism is more negligible in England than in any European country.

Aortic thrombosis—Leriche's syndrome, or aortic thrombosis, is generally considered to be a rare condition, but it is apparently neither as rare nor, in most cases, as dangerous as has usually been thought. Drs. F. Starer and D. Sutton, radiologists at St. Mary's Hospital, London, have recently reported in the *British Medical Journal* on a series of 32 patients with aortic thrombosis who were seen during a four year period. Since the paper was written eight more patients with this condition have been seen, making a total of 40 such patients in five years. It is true that this hospital has a large and active unit specializing in the surgery of peripheral vascular disease and that it draws patients from all over the country. In all 32 patients the diagnosis was confirmed by aortography, which was carried out without complication; the authors believe that the recorded hazards of aortography have been mainly due to faulty technic.

Aortic thrombosis is nearly always caused by atheroma of the lower abdominal aorta and the iliac vessels. The authors consider Buerger's disease and other forms of aortitis, which have been cited as responsible in previous papers, to be of little importance. There was a possible relation to trauma in three patients in this series. In six patients, in whom aortic thrombosis was associated with mitral stenosis, retrograde thrombosis was considered to have followed peripheral emboli. Twenty patients had difficulty dating the onset of symptoms, because they began so gradually. Twelve patients, who experienced a more rapid beginning of their symptoms, could date the origin more definitely.

Intermittent claudication was the outstanding symptom present in nearly all patients in this series; it consisted of an aching or burning sensation brought on by exercise and relieved within a few minutes by rest. In the early stages the pain involved the calf muscles of one leg, beginning after the patient had walked several hundred yards. Gradually, claudication developed within shorter distances, and the pain also involved the opposite calf, thighs and, sometimes, the hips. The full development of this symptom may take years. Loss of power in the legs, frequently accompanied by muscle wasting, was the next most frequent symptom; it occurred, sometimes very severely, in about half the patients in the series.

Leriche stressed the diagnostic significance of impotence in the male, and this was admitted by four patients in the present series. Persistent central backache was a fairly frequent complaint, although its exact incidence could not be assessed. Leriche believed it was due to the intense periarteritis found in relation to the thrombosed segment of aorta. The diminished blood supply to the legs almost invariably resulted in marked coldness of the feet; usually the patients or their spouses were very conscious of this. Exceptions were those patients who had had a previous lumbar sympathectomy; while this operation did not seem to make any difference to the patients' progress, it did, in many cases, result in a warmer skin. The impoverished blood supply also caused dermal trophic changes, sometimes with

(Continued on page A-94)

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Many of your patients probably suffer from brief spells of dejection. Frequently these "letdowns" appear at the same time each day: at 4:30 in the afternoon to the man in his office and at 8:30 in the morning to his wife, after she's seen her husband and children off to work and school.

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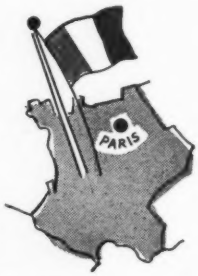
loss of hair, and ridged and deformed toenails; major sequelae such as ulceration and gangrene were uncommon.

The plain roentgenogram is of little significance in diagnosing aortic thrombosis. Aortography is the most useful procedure in making a positive diagnosis, but it involves discomfort to the patient and carries an appreciable morbidity. It is not an examination to be undertaken casually by the inexperienced person, whether radiologist or surgeon. The incidence of complications in aortography does, in fact, appear to be directly related to the experience of the operators. The interpretation of films is, on the whole, straightforward.

FRANCE



Periodic health examinations—Under the terms of the 1945 law which established social security, all residents receive a physical checkup before 18 months and at 4, 10, 14, 21, 30, 40, 50 and 60 years of age. Persons in whom disease is detected are referred to their own physicians for treatment.

Any medical practitioner can perform these examinations, but usually they are done in organized centers with the aid of specialists. In Paris and its suburbs, which have about five million inhabitants, about 120,000 physical examinations are carried out each year at the centers established by the social security fund. An average of 6000 to 8000 of the examined persons are diseased; one-half of these need further tests.

In an article in *Annales de médecine praticienne et sociale*, Dr. André Theil states that three of every thousand persons have tuberculosis. Thirteen per cent have primary infection and 82 per cent have advanced forms of lung tuberculosis; in 1 per cent of patients the disease is outside the lung, and in 3 per cent it has several foci.

The incidence of cancer increased from 14 cases per 100,000 persons in 1949 to 55 per 100,000 in 1956. In practice this means that each year about a thousand patients are suspected of having cancer and are sent to a cancer detection center where the diagnosis is confirmed in about 60 cases.

Syphilis has increased in frequency since 1955, not only among the metropolitan Parisians, but also among the foreigners and the North Africans. The present rate of syphilitic morbidity for these three groups is one, two and four cases per thousand, respectively. Patients suspected of having syphilitic infection are treated or at least put under observation, while those with positive serologic tests but with no clinical signs of syphilis are retested after 15 days. The social service continues to be responsible for these patients.

Two-thirds of the people found to be sick, with the exception of the syphilitics, obey the physician's advice and undergo treatment.

Childhood diabetes and growth—Dr. H. Lestradet (Presse méd. 66:582, 1958) has pointed out that there are two definite types of childhood diabetes. In the first type, hyperadrenocorticism, or Mauriac's syndrome as it is called in France, is present. The child has a moon-shaped face, resembling that of the chronic rheumatic patient who has been treated with cortisone for a long time; excess fat on the neck, chest, abdomen and especially on the buttocks; and a large liver. In addition, these children show signs of osteoporosis and are stunted in growth.

In contrast, the child with the second type of diabetes is lean, delicate, underweight and of less than average height; has a large, smooth, fatty liver; is frequently edematous, and is troubled by conditions of the skin and teeth.

Lestradet, who saw 500 diabetic children, concluded that growth requires an increased rate of protein synthesis which in turn demands abundant consumption of glucides. This process requires an adequate amount of insulin which plays the role of a growth hormone.

The glucides are improperly utilized in spite of the high level of sugar and ketone bodies in the blood, with the result that the glucide deficiency of the cells impedes the utilization and synthesis of the protides. The transformation of the food proteins into glucides further increases the protein deficiency. In some children, this causes hyperadrenocorticism; in others, the result is a low blood protein level, with fattening due to the lack of the lipotropic amino acids.

Lestradet believes that this developmental condition can be entirely avoided by giving a well-balanced diet rich in protides and glucides and administering ample doses of insulin. When a developmental condition does appear, the amount of dietary lipids and glucides must be further increased and fairly large doses of insulin must be given for awhile.

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Through the Stethoscope

WENDELL J. S. KRIEG

My dear son:

I was made very happy on reading your last letter informing me of your decision to spend your life in research and as a professor in medical science. A father is always happy if his son decides of his own free will to enter a line of work similar to his own. So much floods up in response to your request for advice, I am afraid it will take a whole series of letters to say it. I was aware that you were making your decision, and didn't want to influence you.

Yes, I agree that if you are going into the preclinical sciences, the end of your second year of medical school is a good time to make the switch and matriculate for the Ph.D. One really must have studied anatomy, physiology, biochemistry, bacteriology and pathology to handle the problems in any one of these. It's good to have the clinical subjects, too, but that means two years more, and you know how my finances stand. Any dwelling on clinical applications in your teaching will take time away from the main subjects, and your students will spend the rest of their lives in such work. Clinical comments in lectures by young men may ring fresh enough, but each year such remarks are attached to a little experience by a longer and thinner thread. I believe that if you take an M.D., you should practice medicine, which is what the degree prepares you for, not for research. If you are going to spend your career in a science, you should earn a Ph.D. in that subject. Of course, it would be fine to earn both degrees—but expensive.

In choosing a university career, you have allied yourself with that little stream of men who have transmitted, extended and disseminated knowledge and appreciation through the centuries. In the past, professors have not usually been the authors of great books, but they have evaluated, commented on and perpetuated them. The fact that the great works of the intellect were often wrought by men who were struggling with adverse conditions and an unfriendly environment only reflects the bad state of affairs in the narrow and stuffy halls of learning. Such men would have been welcomed in universities today, their work (or at least the workers) supported, and their books a source of pride and prestige. More and more, talent today is being discovered early, encouraged and given a chance to grow. This is paralleled by the increasing specialization and professionalism of learning, the increasing burden of knowing what was done in the past; so I suppose that, in the future, important works are more likely to come from the universities than from men

(Continued on page A-100)

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in private life. I speak of contributions to thought rather than great original works of art and letters, since the men who produce them can never be bought or bound by universities or by anything else. You yourself will admit that we are not concerned with genius right now, but I do say that in a university whatever creative talents and intellectual interests you have can receive their best leavening warmth.

Your opportunity to achieve an adequate background in an atmosphere of detachment will probably be better than mine was. There is a great increase in the number and availability of fellowships in the sciences, and competition is not too keen for them. Most young men qualified for research in the medical sciences go into the more remunerative fields of the practice of medicine, and those who do elect to be graduate students are tortured by their draft boards. Even when they have finished their Ph.D., they must be drafted as privates, while the green M.D. is an officer. With all the eagerness to clear the way for young men in pure science, I cannot see why this impediment has not been removed.

When I began my work, one could either take an assistantship and teach, doing his research on the side, or apply for one of the relatively few fellowships offered by philanthropic organizations. Now the U. S. Public Health Service offers numerous and quite adequate fellowships, so that private agencies are in the anomalous position of competing for beneficiaries.

Salaries will also be better by the time you are trained. Universities have now to compete with industry, and medical schools with the emoluments of medical practice. The current wave of interest in education and in the lot of the teacher should help to increase salaries; but this will be only by government subsidies, in the private universities at any rate, because they have no source to tap. Meanwhile, private universities wishing to please their wealthy trustees and potential benefactors are crying that they do not want government money or interference. This does not represent the viewpoint of the faculty, however.

Fortunately, you chose a subject with a practical application and, more important now, a national urgency. Biologists, astronomers and anthropologists are having as hard a time as ever. As for the humanities and fine arts, I don't see how they are ever going to recover in our businessman's world. They have no industrial applications; endowments are not coming their way, and the government has left them unsupported. If your subject represents a possible way to save lives or destroy them, to create energy or apply it, to simplify physical existence or complicate it, the subject will receive support. If it only makes living more dignified, more comprehensible or more satisfying, it must fend for itself. In spite of the great simplification of the business of living and the cheapness of procuring culture that modern technology has given us, we are still in a materialistic age.

Today, on a small monthly budget you can soon acquire a collection of the finest literature of the ages, albums of impeccable color reproductions of paintings, and flawless recordings of music. Nevertheless, few except women now receive degrees in the liberal or fine arts. Latin, Greek, logic and academic philosophy are dying, and little education for enjoyment of and connoisseurship in the fine arts is given in any college. This is partly because the course of study in the arts has always been so conservative. Literature has been emphasized in the past because of the comfortable, twice-removed quality of the written word and the cheapness of print. No expensive laboratories are required.

The contrast between pure scholarship and the service professions is no new tendency. I have just taken down Burton's "Anatomy of Melancholy," in which I had marked a passage: "All which our ordinary students, right well perceiving in the Universities, how unprofitable these Poeticall, Mathematicall, and Philosophicall studies are, how little respected, how few Pattrons; apply themselves in all haste to those three commodious professions of Law, Physicke, and Divinity, rejecting these arts in the meane time, History, Philosophy, Philology, or lightly passing them over, as pleasant toyes, fitting only table talke, and to furnish them with discourse."

When I took down the book, I noticed it was midnight, so I must stop. When I write you again, I would like to sum up some things I've learned about the conduct of research and creative work.

So, good night,
Father

Deep Venous Thrombosis: A Single Disease

NORMAN B. ROBERG*

University of Illinois College of Medicine, Chicago

NORMAN B. ROBERG

THE continued importance of deep venous thrombosis is emphasized by six developments which have occurred in the past 15 years: (1) The incidence of venous thrombosis has been reported[1,2] to have increased twofold to threefold. (2) The prophylactic and therapeutic value of the anticoagulant drugs has been established.[3-13] (3) The limitations of surgical intervention have become clearer.[14-16] (4) The antibiotics are being used without evidence of either benefit or rationale.[17] (5) The serious sequelae of deep venous thrombosis have been recognized more fully; 20 per cent of the patients with deep venous thrombosis die of pulmonary embolism, and crippling of the lower leg develops in 85 per cent of the survivors.[7,8,14,18] (6) From 1939 to 1955, Ochsner and DeBakey[1,19-22] advanced a concept that deep venous thrombosis consists of two separate diseases, each of which has a different prognosis and a different treatment. The influence of their theory on both prognostication and treatment has led to this inquiry into the nature of deep venous thrombosis, thrombosis occurring in the large, deep veins of the legs in association with operations, childbirth and serious illness.

Ochsner and DeBakey considered that deep venous thrombosis comprises two separate lesions or diseases which rarely coincide: phlebothrombosis and thrombophlebitis. Phlebothrombosis is ascribed to a clot which is not associated with inflammation of the vein, and it results from circulatory stasis and increased coagulability of the blood. The clinical signs are tenderness in the feet, calves and the anteromedial aspect of the thighs, with little or no fever and usually with no swelling. Pulmonary embolism is considered the only danger in this form of venous thrombosis, and ligation of the veins above the thrombi is the only treatment recommended. The anticoagulant drugs are condemned as not preventing pulmonary embolism.

Ochsner[22] gave the definition of thrombophlebitis as a primary inflammation of the

*Associate Professor of Medicine, University of Illinois College of Medicine, Chicago, Illinois.

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vein wall caused "by a perivenous lymphangitis resulting from actual invasion of the perivenous lymphatics either by microorganisms or by toxins." A local inflammation of the vein wall, secondary to the lymphangitis, is said to cause the thrombosis. The clinical signs are familiar: pain, fever and swelling of the leg. "The more severe the infection, the more marked is the febrile reaction."[21] The clot does not become detached and there is no danger of pulmonary embolism. The only treatment recommended is procaine anesthesia of the lumbar sympathetic ganglia, which affords "prompt relief of edema and fever, and in none has there been any evidence of recurrence of edema or other postphlebitic manifestations."[21]

This division of deep venous thrombosis into phlebothrombosis and thrombophlebitis by Ochsner and DeBakey raises several practical questions: (1) Does the fact that venous thrombosis sometimes appears as a mild inflammatory disease of the lower leg, and at other times as a severe inflammatory disease of the entire leg, indicate that these are two different diseases? Or does the variation in extent and intensity of the inflammation represent two stages or extremes in the natural history of a single disease? (2) Is there evidence that the fever, pain and swelling in thrombophlebitis are caused by and proportional to the extent of bacterial infection in and about the vein? (3) Is it correct that there is practically no danger of pulmonary embolism when a marked inflammatory response is present? (4) Is local anesthesia of the lumbar sympathetic ganglia all that is necessary when severe inflammatory thrombosis is present? (5) Are the anticoagulant drugs contraindicated, and is ligation the only way to prevent pulmonary embolism when venous thrombosis occurs with little or no evidence of inflammation? These questions are interrelated and will be discussed both separately and together.

All interested observers agree that the first manifestation of thrombosis may be pulmonary embolism. At other times, the first signs are mild tenderness in the foot and calf, fullness of the veins of the foot and ankle, and slight swelling of the lower leg with or without fever. Other patients have a high temperature and a swollen, painful leg which may be pale or bluish. The majority of workers in this field consider these to be different stages and degrees of a single disease.

Virchow[23] first separated deep venous thrombosis from the frankly suppurative thrombophlebitis which occurs locally in areas of cellulitis such as septic parametritis. He recognized that the common venous thrombosis associated with injury, illness and debility was not related to local infection. Concerning the origin of deep venous thrombosis, Virchow enunciated the triad which is named for him: alterations in (1) the streaming of the blood, (2) the coagulability of the blood, and (3) the wall of the vessel, principally mechanical distortions. He further stated: "What is ordinarily called an infectious phlebitis is neither an infectious process nor a phlebitis, but begins with the formation of a thrombus from the blood." He contended that the natural history of venous thrombosis is the history of the thrombus and that the associated inflammation of the vein was secondary to the presence of the thrombus.

Virchow's studies have been substantiated and extended by Zahn,[24] Bizzozero,[25] Eberth and Schimmelbusch,[26] Welch,[27] Aschoff,[28,29] Roessle,[30] Voegt,[31] Neumann,[32] Frykholm,[33] Wright[34] and McLachlin and Paterson.[35] Among clinicians, Homans,[14] Bauer,[5,6] Zilliacus,[7,8] Fontaine,[36] Byrne,[2] Allen, Barker and Hines[11] and Stoesser and Wels[17] consider venous thrombosis to be a single, noninfectious disease.

Except for some variations in distribution of thrombi within the veins, these pathologists and clinicians agree on the following:

1. The thrombi have a single, uniform and constant development. At their point of origin there is a white "head" of massed platelets and fibrin. On this white head there is added a "neck" of mixed platelets, fibrin, leukocytes and red blood cells. When the vein is almost or completely occluded, a red "tail" is formed. This red tail is essentially a coagulum, consisting of the elements of the blood in their usual proportions.

2. The thrombi start in either the small tributary veins of the feet, calves and adductor muscles of the thigh, or murally in the large veins at points of turbulent blood flow. Such turbulence exists in the pockets of the valves and at the mouths of tributary veins.

3. The thrombi grow into the larger veins, more thrombus being formed from the blood streaming past it, or from tributary veins entering above an occluding thrombus.

4. The coagulum can extend rapidly toward the heart, suddenly occupying and occluding the segments mechanically narrowed by the ligamentous barriers of the soleus muscle, adductor canal and inguinal ligament.

5. Multiple independent thrombi can be found in the same vein or in different veins of one or both legs.

6. In the same vein or in different veins, the clots may lie almost loose with little attachment, or they may be fixed to the vein wall by an intense inflammatory reaction.

7. Though varying in the extent, degree and time required, thrombosis progresses from the smaller tributaries into the deep veins of the calf and thigh.

8. The slower the growth of the clot and the longer it remains in contact with the vein wall, the greater is the inflammatory reaction. Inflammatory fixation probably occurs after 24 to 48 hours of contact between clot and vein wall.

9. If a clot breaks off, pulmonary embolism ensues. Where the clot becomes fixed, the inflammatory reaction destroys the effectiveness of the valves of the femoral veins; later, edema and induration of the lower leg will occur. Both processes, the formation of emboli and the inflammatory destruction of the vein, occur simultaneously in the same veins. What Ochsner and DeBakey have termed phlebothrombosis and thrombophlebitis are two stages of one disease, with the late inflammatory stage developing if the patient does not have or if he survives pulmonary embolization.

10. Seldom are significant lesions found in the veins at the points of origin of the thrombi.

11. There is no evidence of bacterial infection of the vein in deep venous thrombosis. The pathologists caution against attributing etiologic significance at autopsy to the presence of bacteria in or about thrombi.

The preponderance of opinion is that venous thrombosis, with its varying degrees and extents of reaction and occlusion, is a single disease, and that the inflammatory reaction is not infectious. What evidence of a bacterial origin of thrombophlebitis did Ochsner and DeBakey present? In a series of their papers, they did not give evidence from their own material that bacteria or bacterial toxins are present. Their supporting references do not substantiate a bacterial origin of deep venous thrombosis. The translations from French and German sometimes are inexact and, at other times, incomplete. I would now like to mention briefly their pertinent references.

They quote Rokitansky,[37] who, during the prebacteriologic era, divided thrombosis into a primary phlebitic and a primary thrombotic form. However, it is adequately clear, from the original text, that Rokitansky was describing suppurative thrombophlebitis and deep spontaneous venous thrombosis rather than two forms of deep venous thrombosis.

Koester,[38] quoted by Kaufmann[39] and apparently confused with Koster,[40] described suppurative bacterial thrombophlebitis in 1875. Kaufmann and Benda[41] also described the classic suppurative thrombophlebitis continuous with the cellulitis of the surrounding tissues, but they separated this now uncommon entity from deep venous thrombosis, which they termed "bland," "spontaneous" or "distant" thrombosis. Koster's paper does not deal with bacterial infection. Ritter[42] quoted only the unconfirmed observations of Rosenow[43] as evidence for bacterial participation in deep venous thrombosis. Govaerts[44] also quoted Rosenow, but criticized specifically the theory of infectious spontaneous postoperative venous thrombosis. In 1932, Homans[45] did favor a nonsuppurative lymphangitis of the iliofemoral sheath as the cause of thrombophlebitis. However, by 1947,[14] he considered the inflammatory and noninflammatory forms to be different stages and degrees of the same disease. Aschoff[28] stated that there was no evidence of an infectious origin of the disease. He did not say that the white thrombus and the red throm-

bus occurred separately or under different conditions. Thus, Ochsner and DeBakey did not present from their own material or in supporting references evidence of an infectious, bacterial origin of deep venous thrombosis.

Epidemiologic evidence speaks against the bacterial theory. Werthemann and Rutishauser[46] noted at autopsy during both world wars the decrease in pulmonary embolism to one-third the usual incidence. During war, the populace being defeated has more rather than less infectious disease. Aschoff expressed disappointment that the era of aseptic surgery brought no decrease in venous thrombosis and pulmonary embolism. Ochsner and DeBakey[1] reported an increase in thrombosis and embolism from 131 to 241 per 100,000 admissions in New Orleans between the periods of 1938 to 1942 and 1946 to 1950. Byrne[2] reported the incidence of phlebitis in Boston as 1.3 per 1000 admissions in 1943 and 3.9 per 1000 in 1951. Only part of these increases may be ascribed to increased interest and diagnostic ability. Thus, the present era of relatively aseptic and atraumatic surgery, of lessened endemic and epidemic infection, and of antibiotic therapy has witnessed an increase rather than a decline in venous thrombosis and pulmonary embolism. It may well be that the rising age of the populace, with the concomitant relative increase in heart disease and neoplasia, is significant. Patients with cardiovascular disease and those undergoing radical surgery for neoplasia are especially susceptible to deep venous thrombosis.

If there is no pathologic, clinical or epidemiologic evidence for bacterial infection of the veins in deep venous thrombosis, may it be that some other form of primary venous inflammation plays an important role? Clinical evidence indicates that the inflammatory reaction is not primary. Bauer[5, 6] and Zilliacus[7, 8] observed that treatment with heparin reduced the duration of fever from an average of 23.3 days to 8.4 days. By procaine anesthesia of the lumbar sympathetic ganglia, Ochsner and DeBakey[21] shortened the duration of fever to two days in 65 per cent of patients, and another 31 per cent were afebrile within three to eight days. Homans[14, 45] reported striking improvement shortly after thrombectomy in acute phlegmasia alba dolens. Fontaine[36] has had similar experience with both heparin and thrombectomy. Using DICUMAROL® prophylactically in more than 3500 predisposed postoperative patients, Barker, Allen and co-workers[9, 11] reduced thrombosis and embolism from an expected 3 to 5 per cent incidence to only 0.1 per cent. With similar postoperative prophylaxis, Hartenbach[12] reduced venous thrombosis from 4.83 to 0.31 per cent and fatal pulmonary embolism from 1.83 to 0.16 per cent. Such dramatic shortening of the duration of fever and diminution in thrombosis and embolism would not be expected from procaine, from the anticoagulants, or from the surgical removal of the thrombi if either local infection or inflammation were primary in deep venous thrombosis. The benefit of these different forms of treatment is further evidence that the inflammatory response results from the presence of the thrombus.

The literature does not confirm Ochsner and DeBakey's impression that pulmonary embolism occurs only rarely in the inflammatory forms of venous thrombosis. Barker et al.[47] reported a death rate of 14.9 per cent from pulmonary embolism among 227 patients with obvious thrombophlebitis. Byrne[2] found the death rate from pulmonary embolism to be 53 per cent among patients with minimal calf tenderness and edema, and 55 per cent among patients with severe bilateral thrombophlebitis.

Death rates of 14.9 per cent and 55 per cent from pulmonary embolism in the presence of frank thrombophlebitis suggest that procaine anesthesia of the lumbar sympathetic ganglia may not be adequate protection. On the other hand, Barker, Bauer and Zilliacus reported not only good immediate improvement with the anticoagulants but also a virtual elimination of fatal pulmonary embolism, regardless of the stage and extent of the venous thrombosis. Ochsner and DeBakey did not report any reexamination of their patients after 5 to 10 years. The reports of Bauer, Zilliacus and Hoejensgard showed that 85 per cent of patients, 6 to 31 years later, have serious postphlebitic sequelae in the lower leg. With prompt anticoagulant therapy during the acute disease,

especially before the thrombosis has spread to the upper leg, only 7 per cent of patients had moderate edema and induration after 10 years. Just as deep venous thrombosis cannot be divided into phlebothrombosis and thrombophlebitis on the bases of local clinical manifestations and the nature of the clot, so the occurrence of pulmonary embolism and the late sequelae indicate the presence of a single disease.

Aside from their therapeutic value, the action of the anticoagulant drugs confirms the opinions of clinicians and pathologists that deep venous thrombosis is a single process with variable and unpredictable degrees of inflammatory fixation of the clot. The anticoagulant drugs promptly relieve fever, pain and swelling. They prevent spread from the lower to the upper leg, prevent pulmonary embolism, and greatly reduce the late sequelae of induration and ulceration. It is the propagating coagulum which kills by pulmonary embolism or cripples by destroying the function of the femoral veins. One returns to Virchow's dictum that the natural history of venous thrombosis is that of the thrombus. The anticoagulants are the specific antagonists of the development and growth of this coagulum, and thus of the development and progression of the disease which it causes.

What is the role of ligation of the veins? Since deep venous thrombosis is usually bilateral, and fatal emboli may come from either the superficial or the deep femoral veins, bilateral common femoral vein ligation is the logical procedure. Ligation of the external iliac veins causes less circulatory disturbance than does ligation of the common femorals and, obviously, inferior vena caval ligation protects the patient from multiple small emboli originating in the pelvic veins.

Ligation of the inferior vena cava has serious late sequelae. Ray and Burch[48] and DeCamp et al.[49] observed persistent elevation of the venous pressure in the legs following ligation of the inferior vena cava. Shea and Robertson[15] found that only one of 25 patients had normal legs five years after caval ligation. Bowers and Leb[16] were alarmed by the development of ulcers in the "normal" leg in 15 of their 24 patients within five years of such ligation. From the Swedish experience, these serious sequelae should be much greater 10 to 20 years after inferior vena caval ligation. It is obvious that ligation of the inferior vena cava prevents pulmonary embolism from below the ligature, but does not prevent the destructive progression of the disease below the site of ligation. In 1947, Homans was concerned by the serious degree of stasis and edema following common femoral vein ligation. He regarded inferior vena caval ligation as a last resort to save life when both anticoagulants and peripheral ligation failed to prevent further pulmonary embolism. His judgment was sound; it has been confirmed by occurrence of the serious sequelae just noted, and it continues to be good advice.

Conclusions

1. Deep venous thrombosis is a single disease caused by a single form of thrombus. The propagating portion of the thrombus is essentially a coagulum of whole blood. It is this coagulum which either kills 20 per cent of the patients by pulmonary embolism or cripples 85 per cent of the survivors by the later development of edema, induration or ulceration. Originating usually in the lower legs, the clot grows upward. The inflammatory reaction in the vein generally is proportional to the extent of the coagulum and the length of time it is in contact with the vein.

2. There is no evidence for separating venous thrombosis into two diseases on the basis of inflammatory response, prognosis or treatment. The phlebothrombosis and thrombophlebitis of Ochsner and DeBakey are generally recognized as being two stages or degrees of a single process, usually occurring together at the same time or at different times in the same patient, with both stages causing fatal pulmonary embolism and serious late crippling.

3. There is no evidence that local bacterial infection plays any role in deep venous thrombosis. There is no indication for the use of antibiotics for the fever, pain and swelling which are caused by the sterile coagulum.

4. Ligation of the inferior vena cava is not a treatment for deep venous thrombosis. Such

ligation is a treatment of last resort to prevent recurrent pulmonary embolization when the anticoagulant drugs are contraindicated or do not prevent further embolism.

5. It is the propagating "red tail" which kills and cripples. This propagating portion of the thrombus is essentially a coagulum of whole blood. The anticoagulants specifically can prevent the formation of the coagulum, stop its growth from the lower to the upper leg, prevent its development to a size capable of causing serious pulmonary embolism, and prevent the destruction of the valves of the femoral veins by the inflammatory reaction to the clot.

6. Aside from their prophylactic and therapeutic value, the anticoagulant drugs have confirmed the single nature of deep venous thrombosis. By preventing all manifestations of deep venous thrombosis and by stopping such progressive manifestations as local thrombosis, pulmonary embolism and late edema and ulceration, these drugs have confirmed Virchow's statement of 100 years ago: "The natural history of thrombosis is above all the natural history of the thrombus."

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A Rational Approach to Antibiotic Therapy of Childhood Infections

C. HENRY KEMPE*

University of Colorado School of Medicine, Denver

C. HENRY KEMPE

ANTIBIOTICS have revolutionized medical care in our lifetime. It is likely that we will see, in the next few years, newer antibiotics which will be effective against the host of viral diseases not now amenable to specific therapeutic measures.

If we use antibiotics intelligently, if we have some respect for their potency and their worth, if we appreciate their expense, and above all if we do no harm with them, our practice can be immeasurably enriched and our care improved. Advertising claims made for each new antibacterial agent, alone and in combinations, are always unduly enthusiastic and sometimes misleading. The physician is constantly faced with free samples and the bewildering array of persuasive literature featuring such terms as synergism, potentiation, low toxicity, no emergence of resistant strains, sure-fire bactericidal action, broadest spectrum, and so on. At last count there were 69 antibacterial preparations on the market which contained two, three, four or five antibiotics in fixed combination.

The dangers of the overuse of antibiotics are clear. They are (1) *hypersensitivity*, a problem of adult medicine which is becoming most alarming with as many as 3 to 7 per cent of our adult population acutely sensitive to penicillin; (2) *direct drug toxicity*, an immediate problem in terms of vomiting, nausea, diarrhea in many instances, or pruritus ani, which is, I am sure, a sensitivity response rather than a response to monilial infection; (3) *alteration of the normal flora*, with over-

*Professor of Pediatrics and Head of the Department of Pediatrics, University of Colorado School of Medicine, Denver, Colorado.

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growth of *Monilia, Proteus, Pseudomonas* or hemolytic staphylococci, the latter causing a devastating and terribly dangerous complication in the form of staphylococcal enteritis; (4) *masking of serious disease* which does not become apparent until therapy does not seem to work 5 to 10 days later. This is a problem we see a good deal in patients who are eventually going to be diagnosed as having subacute bacterial endocarditis or osteomyelitis; (5) lastly, the increasing *selection of bacterial variants* which are resistant. As new antibiotics come along, we quickly make them useless to us by their overuse. I shall have more to say about this later.

Fever is only a symptom, and it is a symptom of many diseases *other* than bacterial infections. Fever is, of course, a prominent symptom in viral respiratory infections which are insusceptible to antibiotic therapy at present. The use of antibiotics in the treatment of fever without making a clinical diagnosis of a bacterial disease invariably results in our regarding these drugs as antipyretics rather than antimicrobials—as forms of better aspirin rather than what they truly are. We constantly assume that a drug is no good if the fever fails to drop promptly, and this leads to the quick addition of a second and a third antibiotic. All of us face the problem of no longer knowing the natural history of many diseases. Expecting a decisive response in fever within 24 hours may be completely unreasonable considering the disease at hand, the location of the bacterial organisms, and the possible chances of clearing up the infection within a short time.

Our plea, then, is for etiologic orientation and the making of a presumptive clinical diagnosis. One should ask oneself these questions: (1) Is this a bacterial disease, and, if so, what is the likely bacterial agent causing the disease? (2) Where are the bulk of the organisms located? (3) How can I get at them with maximal concentration of the antibiotic agent?

It is by no means always necessary to identify the organism through the usual bacteriologic laboratory. In our clinical practice we are quickly able to make fairly justified clinical diagnoses of such things as streptococcal or pneumococcal tonsillitis, and common urinary tract infections due to *Escherichia coli, Aerobacter*, and others. All these do not require bacteriologic diagnosis; they all can be made by clinical means. On the other hand, it is becoming increasingly popular for physicians in general practice and pediatrics to do their own bacteriologic examination in their own offices. It is now possible to purchase sterile media by mail at a very reasonable cost of less than 50 cents a plate (Hyland Laboratories). Simple egg incubators costing less than $50 complete the necessary armamentarium (Montgomery Ward, Sears Roebuck & Co.). There is no question that antibiotic therapy can be more effective and clinical practice more enjoyable when simple bacteriologic diagnostic means are readily available to the physician in his own office.

One of the greatest aids in differentiating respiratory diseases, bacterial versus viral, is to see family outbreaks. One is not apt to mistake the common cold or influenza for bacterial disease, because one sees three or four members in the household with the same clinical entity. Streptococcal and pneumococcal disease, on the other hand, frequently presents a variety of distinct clinical pictures in a given family group.

The location of the organisms, of course, is another most important point, because it is essential to bring the pathogen and the antibiotic together. Rational use of antibiotics requires some knowledge of the most effective route by which one can accomplish this. All of us desire to get our patients well as quickly as possible, and all of us desire to be completely up to date, and therefore we are usually tempted to try everything new as fast as it comes along. Nothing could be more dangerous. It is a sobering fact that when the first fatal hematologic complications of chloramphenicol therapy occurred it was discovered that one out of three of the youngsters were physicians' children who had received the medication from their own fathers, who had tried their free samples.

The use of antibiotics prophylactically in pediatric surgery is another area which gives us cause for concern. It is not surprising, since

a likely pathogen in a given operation cannot be predicted, that prophylactic antibiotic therapy seems to do far more harm than it does good. In a recent study of 250 clean surgical patients, only 14 of 154 patients who did not receive antibiotic therapy ever had a specific indication for it. The incidence of bacterial complications among these 154 patients was 7.8 per cent. Among the prophylactically treated group of 96 patients, bacterial complications developed in 37.5 per cent *while they were receiving antibiotic therapy*. These findings are in agreement with our own experience and that of others. In our experience, bacterial complications in clean operations are five times as high in prophylactically treated patients as they are in patients who are not given antibiotics prophylactically.

I think it is time we realized that it is impossible to bacterially sterilize a child. It simply cannot be done. No matter how many antibiotics one gives, it is impossible to get rid of every bacterium. The more we give and the more we try to eliminate the bacteria, the more chance we provide for the one, two or five remaining ones to overgrow and become pathogenic, whereas in the natural way of things they would not be pathogenic.

I would like to say a few words about use of antibiotics in treatment of families.[1] No one can deal with children and families long without realizing that it is futile and irrational to treat a given child week after week and have relapses occur, without ever taking a good look at the whole family. Family physicians are in a unique position to do sensible antibiotic family therapy if they once become aware of the family reservoir of bacterial infections. There is little one can do about viral family infections such as gastroenteritis, the common cold and influenza, but when it comes to staphylococcic and streptococcic and pneumococcic family infections there is a good deal one can do by adequate treatment of all family members.

Choice and Dosage of Common Antibiotics

Antimicrobial drugs are classified as bactericidal (those which kill bacterial organisms) or bacteriostatic (those which primarily inhibit bacterial multiplication, which, however, resumes when the bacteriostatic drugs are removed). Bactericidal agents actually differ from bacteriostatic agents only in the fact that their action is irreversible. The difference between bacteriostatic and bactericidal actions appears to be quantitative rather than qualitative. Agents may be bacteriostatic at a given concentration and for a given exposure, while increasing concentration or exposure may cause a progressive shift toward bactericidal action.

Primarily bactericidal agents in current use are penicillin, streptomycin, polymyxin B, bacitracin, neomycin and ristocetin. Primarily bacteriostatic agents are tetracycline and all related compounds, chloramphenicol, erythromycin, novobiocin and all sulfonamide drugs. Pediatric dosages of these drugs are given in table 1.

A simple way to recall the antibacterial spectrum of antibiotics is as follows. Pathogens are divided into rods (most of which are gram-negative) and cocci (most of which are gram-positive). Bactericidal agents which kill rods only are streptomycin and polymyxin B. Bactericidal agents which kill cocci only are penicillin, bacitracin and ristocetin. Neomycin is bactericidal for a wide variety of rods and cocci. Bacteriostatic agents affecting cocci only are erythromycin and novobiocin, while all "broad-spectrum" antibiotics are bacteriostatic for both rods and cocci. Table 2 reviews the antimicrobial spectra of these drugs, and table 3 lists their toxic effects.

Polymyxin, Bacitracin and Neomycin

Polymyxin, bacitracin and neomycin are powerful bactericidal drugs. Their parenteral use is limited to hospitalized patients and to infections not responding to other antibacterial therapy. While there is a certain amount of toxicity associated with these agents, our experience has shown this to be much less common in children than in adults. In the dosages listed and for the durations outlined, use of these drugs is frequently lifesaving in the management of patients with serious bacterial disease.

TABLE 1

PEDIATRIC DOSAGES OF ANTIBIOTICS AND CHEMOTHERAPEUTIC AGENTS

	ORAL	PARENTERAL	
		Intramuscular	*Intravenous*
Penicillin	100,000 to 300,000 units five times daily, one-half hour before meals	10,000 units per pound or 100,000 to 300,000 units per day	10,000 units per pound per day
Penicillin V	100,000 to 300,000 units four to five times daily		
Benzathine penicillin G (BICILLIN®, PERMAPEN®, DUAPEN®)	300,000 units four times a day	600,000 units or 1,200,000 units, single injection	
Streptomycin, dihydrostreptomycin	20 mg. per pound per day (in four doses)	10 to 20 mg. per pound per day (in two or three doses)	
Chlortetracycline (AUREOMYCIN®)	10 mg. per pound per day (in four doses)		6 mg. per pound per day (1 mg. per cubic centimeter)
Oxytetracycline (TERRAMYCIN®)	10 to 20 mg. per pound per day (in four doses)	6 mg. per pound per day (in two doses)	6 mg. per pound per day (in two doses)
Tetracycline (ACHROMYCIN®, TETRACYN®, PANMYCIN®, POLYCYCLINE®)	10 to 20 mg. per pound per day (in four doses)	6 mg. per pound per day (in two doses)	6 mg. per pound per day (1 mg. per cubic centimeter) (in two doses)
Chloramphenicol (CHLOROMYCETIN®)	30 to 90 mg. per pound per day (in four doses)	30 to 60 mg. per pound per day (in two doses)	15 to 30 mg. per pound per day (5 mg. per cubic centimeter) (in two or three doses)
Erythromycin (ERYTHROCIN®, ILOTYCIN®)	15 to 30 mg. per pound per day (in four doses)		16 mg. per pound per day (0.5 to 1 mg. per cubic centimeter) (in two doses)
Novobiocin (ALBAMYCIN®, CATHOMYCIN®)	10 to 20 mg. per pound per day (in four doses)	8 to 15 mg. per pound per day (in two doses)	8 to 15 mg. per pound per day (in two doses)
Ristocetin (SPONTIN®)			12 mg. per pound per day (in two doses, diluted)
Neomycin (MYCIFRADIN®)	50 mg. per pound per day (in four doses)	4 mg. per pound per day (in four doses)	
Polymyxin (AEROSPORIN®)	5 to 10 mg. per pound per day (in four doses)	1 mg. per pound per day (in three doses)	
Bacitracin	1000 units per pound per day (in four doses)	300 to 600 units per pound per day. Never over 50,000 units per day (in three doses)	
Sulfisoxazole (GANTRISIN®)	60 mg. per pound per day (in four doses)	60 mg. per pound per day (in three doses)	60 mg. per pound per day (50 mg. per cubic centimeter)

TABLE 1 *(Continued)*

PEDIATRIC DOSAGES OF ANTIBIOTICS AND CHEMOTHERAPEUTIC AGENTS

	TOPICAL			
Subcutaneous	*Intrathecal, intraventricular*	*Aerosol*	*Eye and skin*	*Intrapleural, intra-articular*
	5 to 10 cc. every 24 hours (1000 units per cubic centimeter)	2 cc. four times a day (50,000 units per cubic centimeter)	500 to 1000 units per cubic centimeter	10,000 to 20,000 units per cubic centimeter
	Streptomycin only: 0.5 mg. per pound or 20 mg. per day (5 mg. per cubic centimeter)	2 cc. four times a day (150 mg. per cubic centimeter)	50 mg. per cubic centimeter	50 mg. per cubic centimeter
			5 mg. per cubic centimeter; 30 mg. per gram	5 mg. per cubic centimeter
		1 cc. twice a day (50 mg. per cubic centimeter in 75 per cent propylene glycol)	5 mg. per cubic centimeter; 30 mg. per gram	5 mg. per cubic centimeter
				5 mg. per cubic centimeter
15 to 30 mg. per pound per day (2.5 mg. per cubic centimeter) (in three doses)			5 mg. per cubic centimeter; 10 mg. per gram	5 mg. per cubic centimeter
			5 to 10 mg. per gram	1 mg. per cubic centimeter
		2 cc. four times a day (50 mg. per cubic centimeter)	2 mg. per cubic centimeter; 5 mg. per gram	2 mg. per cubic centimeter
	Under two years, 2 mg. per day; over two years, 5 mg. per day (0.5 to 1 mg. per cubic centimeter)		5 mg. per cubic centimeter	1 mg. per cubic centimeter
	500 to 5000 units per day (1000 units per cubic centimeter)		500 units per cubic centimeter	1000 units per cubic centimeter
60 mg. per pound per day (25 mg. per cubic centimeter)			40 mg. per cubic centimeter	

TABLE 1 *(Continued)*

PEDIATRIC DOSAGES OF ANTIBIOTICS AND CHEMOTHERAPEUTIC AGENTS

	ORAL	PARENTERAL	
		Intramuscular	*Intravenous*
Sulfadiazine, sulfamerazine (or sodium salts)*	60 mg. per pound per day (in four doses)		60 mg. per pound per day (50 mg. per cubic centimeter)
"Mixed sulfas"†	60 mg. per pound per day (in four doses)		
Succinylsulfathiazole (SULFASUXIDINE®)*	100 mg. per pound per day (in four doses)		
Thiazosulfone sodium (PROMIZOLE®)	0.5 to 6 gm. per day (in four doses)		
Nitrofurantoin (FURADANTIN®)	3 to 5 mg. per pound per day (in four doses)		2.2 to 3.2 mg. per pound per day (in two doses, diluted)
Isoniazid (INH) (NYDRAZID®)	8 mg. per pound per day (in two doses)	5 mg. per pound per day (in two doses)	
Aminosalicylic acid (PAS)	2 to 8 gm. per day (in four doses)		2 to 8 gm. per day (30 mg. per cubic centimeter)
Nystatin (MYCOSTATIN®)	Under two years, 400,000 to 800,000 units; over two years, 1 to 2 million units (in three doses)		

*Initial dose should be twice subsequent doses.
†Many combinations available.
(From "Handbook of Pediatrics," by Silver, Kempe and Bruyn. Ed. 2. Los Altos, California, Lange Medical Publications, 1957.)

Polymyxin B (Aerosporin)

Polymyxin B is administered parenterally in the treatment of sepsis, meningitis, or urinary tract infections due to gram-negative organisms such as *Ps. aeruginosa (Bacillus pyocyaneus)*, *Esch. coli*, *A. aerogenes*, *Klebsiella pneumoniae*, and *Hemophilus influenzae*. It is used orally in treatment of intestinal infections due to *Pseudomonas* and *Shigella* when present as pathogens.

Polymyxin B is especially useful in the treatment of serious *Ps. aeruginosa* infections, as usually no other antibiotic can be successfully employed.

Dosage—See table 1.

Oral administration—Consistent absorption does not result when polymyxin B is administered orally, and therefore by this route the drug is never effective in treatment of systemic infections; it is only effective in certain intestinal infections due to susceptible organisms. It will not, alone, sterilize the intestinal tract, as it does not affect gram-positive organisms. The drug is well tolerated when crushed in maple sirup or jam. Larger doses can be used with impunity since the drug is essentially unabsorbed from the intestinal tract. It is best given with neomycin or bacitracin.

Intramuscular administration—The intramuscular route is preferred for systemic, meningeal and urinary tract infections. Injection should be made deep in the upper outer quadrant of the buttocks. To minimize pain at the site of injection, procaine hydrochloride solution is utilized in making dilutions. Five milliliters of sterile salt and 0.5 ml. of 1 per cent procaine solution are added to a bottle containing 50 mg. polymyxin B; 1 ml. equals 10 mg. polymyxin B.

TABLE 1 *(Continued)*

PEDIATRIC DOSAGES OF ANTIBIOTICS AND CHEMOTHERAPEUTIC AGENTS

	TOPICAL			
Subcutaneous	*Intrathecal, intraventricular*	*Aerosol*	*Eye and skin*	*Intrapleural, intra-articular*
60 mg. per pound per day (25 mg. per cubic centimeter)			50 mg. per gram	
			100,000 units per gram	

Note—Toxic reactions are given in table 3. In our experience they are reversible and do not call for discontinuance of the drug.

Local administration—The intrathecal route is required to supplement systemic medication for meningeal infections with *Pseudomonas* or other organisms susceptible to polymyxin B. The drug is practically nonirritating to the meninges in the doses indicated. Intrathecal therapy alone has been successful in prolonged treatment of *Pseudomonas* meningitis. Treatment has been continued in some instances for 8 and 12 weeks.

Intrapleural route, intra-articular administration, etc.—Local irrigation is essential for successful eradication of susceptible bacteria.

Bacitracin

Bacitracin frequently is effective against gram-positive organisms resistant to penicillin, especially in infections of skin, mucous membrane, wounds and burns. It is sometimes synergistic with penicillin and streptomycin.

Dosage—See table 1.

Intramuscular use—Systemic infections with gram-positive organisms require intramuscular administration. Dissolve 50,000 units in 2 per cent procaine in isotonic saline to a final concentration of 10,000 units per milliliter. The injection site must be rotated through four areas, the best areas being those high in the upper outer quadrant of the buttocks below the crest of the ilium.

Caution—Toxic reactions are noted in table 3. Urine should be kept at a pH above 6 by the administration of sodium bicarbonate with each dose. A high urinary output should be maintained by encouraging fluid intake or administering fluid by subcutaneous or intravenous routes. Administration should not be unduly prolonged and usually is discontinued three days after the temperature has reached normal and all local signs of infection have disappeared.

Topical use—For mixed infections, for gram-positive and gram-negative organisms,

TABLE 2

Antimicrobial Spectra of Chemotherapeutic Agents

−+++—Very effective therapeutic agent.
++—Moderately effective therapeutic agent.
+—Slightly effective.

C—Use only in combination with another drug.
at—Antitoxin or antiserum.

	PENICILLIN	STREPTOMYCIN AND DIHYDROSTREPTOMYCIN	TETRACYCLINES	CHLORAMPHENICOL	ERYTHROMYCIN	NOVOBIOCIN	BIOSYNTHETIC (SPONTIN)	*Caution** NEOMYCIN	POLYMYXIN	BACITRACIN	SULFONAMIDES	NITROFURANTOIN (FURADANTIN)
Actinomyces species	+++C	+	+	+++C					+C		++C	++
A. aerogenes		++	++	++				+++	++		+	
Anthrax bacillus	++C	++	++	++							+C	
Brucella species		++C	++C	+C	+C			+	+		+C	
Vibrio cholerae		+	+	+							+	
Clostridium (Cl. tetani)	++C, at		++C, at	++C, at	++C, at			+++			+C, at	
Corynebacterium diphtheriae	+++C, at		++C, at	++C, at	+++, at							
Donovan body (granule, inguinale)		+	++	++								
Erysipelothrix rhusiopathiae (erysipeloid)	+++	+	+									
Esch. coli		++	++	+++				+++	++		++	++
Gonococci	+++	+	+++	+++	+++C						++	
H. ducreyi		+	+++	++	++				+	++	+	
H. influenzae		+++C	++C	+++C	++C				++	+++	++C, at	
H. pertussis		+	++	++	++				+		+C, at	
Klebsiella species (Friedländer's)		+++	++	++				++	+++		+	
Leptospira (Weil's disease)	+	+	++	+	+C			+				
Lymphopathia venereum virus	+		+++	+++	++C						+	
Meningococci	++		++	++							+++C	
Mycobacterium tuberculosis		+++C†									‡	
Pasteurella tularensis		+++	+++	+++				+			+	
Past. pestis (plague)		+++C	+++C	+++C							+C	

TABLE 2 *(Continued)*

ANTIMICROBIAL SPECTRA OF CHEMOTHERAPEUTIC AGENTS

Past. pestis (plague)		+++C	+++C	+++C				+			+		
											+C		

TABLE 2 *(Continued)*

ANTIMICROBIAL SPECTRA OF CHEMOTHERAPEUTIC AGENTS

+++—Very effective therapeutic agent.
++—Moderately effective therapeutic agent.
+—Slightly effective.

C—Use only in combination with another drug.
at—Antitoxin or antiserum.

	PENICILLIN	STREPTOMYCIN AND DIHYDROSTREPTOMYCIN	TETRACYCLINES	CHLORAMPHENICOL	ERYTHROMYCIN	NOVOBIOCIN	BISTOGETIN (SPONTIN)	*Caution** NEOMYCIN	POLYMYXIN	BACITRACIN	SULFONAMIDES	NITROFURANTOIN (FURADANTIN)
Pneumococci	+++		+++	+++	+++C					+++	+	
Primary atypical pneumonia virus			+++	++	++C							
P. vulgaris		++	+	+		+++C		+++			+C	+++
Ps. aeruginosa		+	+	+				++	+++			+++
Psittacosis virus	++		+++	+++	+C						+	
Rickettsiae (Rocky Mountain spotted fever, Q fever, typhus)			+++	+++	+C							
Salmonella typhi			+	+++				+			+	
Shigella		+	+++	+++					++		++	
Spirochetes												
Borrelia recurrentis	++		+++	++	++C			+		+		
Vincent's bacillus	++				++							
Treponema pallidum	+++		++	++	+C			+		+		
Spirillum minus	+		+++	++	++			+				
Staphylococci	++C	+	++	++	+++C	+++C	+++	+++		+++	+	++
Streptobacillus moniliformis (rat-bite fever)	++		+									
Streptococci												
Beta hemolytic	+++	+	++	++	+++C		+++	+++		+++	+	
Alpha hemolytic *(Str. viridans)*	++	+	++	++	+++C		+++	+++		+++		
Enterococci *(Str. faecalis)*	++C	++C	+C	++C	++C		+++	+++		+++		

*These agents are nephrotoxic when used systemically and should be so used in hospitalized patients only.
†Combined therapy with streptomycin or isoniazid (INH) or both and para-aminosalicylic acid (PAS).
‡The sulfone compounds are also effective: glucosulfone (PROMIN®), sulfoxone (DIASONE®), and thiazosulfone (Promizole).

TABLE 3

TOXIC REACTIONS OF CHEMOTHERAPEUTIC AND ANTIBIOTIC AGENTS

Penicillin, benzathine penicillin G (Bicillin, Permapen, Duapen)	Allergic reactions are rare in children. Fever, anaphylaxis, depression of marrow, mycotic stomatitis
Streptomycin	Damage to vestibular apparatus, rash, fever, depression of marrow
Dihydrostreptomycin	Damage to eighth nerve (deafness)
Chloramphenicol (Chloromycetin)	Aplastic anemia; other as under tetracyclines
Oxytetracycline (Terramycin), chlortetracycline (Aureomycin), tetracycline (Achromycin, Tetracyn, Panmycin, Polycycline)	Vomiting, diarrhea, stomatitis and glossitis. Overgrowth of resistant organisms *(Monilia, Staph. aureus, Pseudomonas, Proteus)*
Erythromycin (Erythrocin, Ilotycin)	Nausea, vomiting, monilial infections, drug fever
Novobiocin (Cathomycin, Albamycin)	Drug fever, pruritic skin eruption, marked eosinophilia, granulopenia
Ristocetin (Spontin)	Skin eruption, diarrhea, drug fever, neutropenia
Polymyxin (Aerosporin)	Headache, hypesthesia, fever. Albuminuria and cylindruria. Elevated nonprotein nitrogen
Neomycin (Mycifradin)	Oral or topical use is harmless. Intramuscular use should not exceed 10 days. In prolonged use or high dosage, eighth nerve damage (deafness) is irreversible. Nephrotoxicity is transient unless previous renal impairment existed
Bacitracin	Oral or topical use is harmless. Intramuscular use may produce signs of transient nephrotoxicity, nausea and vomiting
Sulfisoxazole (Gantrisin); sulfadiazine, sulfamerazine, or sodium salts; "mixed sulfas"*	Skin eruption, fever, bone marrow depression. Adequate fluid intake and alkaline urine decrease chances of oliguria and hematuria
Succinylsulfathiazole (Sulfasuxidine)	Minimal absorption if bowel mucosa intact
Thiazosulfone (Promizole)	Vomiting, methemoglobinemia, leukopenia, thyroid enlargement, premature development of secondary sex characteristics
Nitrofurantoin (Furadantin)	Malaise, nausea, skin eruptions. Maximal continuous course 14 days. Central nervous system disturbances (give calcium intravenously). Give B complex
Isoniazid (INH)	Constipation, hyperreflexia. May aggravate epilepsy. Give pyridoxine
Aminosalicylic acid (PAS)	Gastric irritation and vomiting, anorexia. Sodium salt may be substituted and dose decreased

*Sulfonamide mixtures are less likely to cause toxic reactions than the same dose of a single sulfonamide.
(From "Handbook of Pediatrics," by Silver, Kempe and Bruyn. Ed. 2. Los Altos, California, Lange Medical Publications, 1957.)

for burn dressings, or for irrigation of wounds, the drug is applied topically. It may be applied locally combined with polymyxin B.

Oral administration—In combination with neomycin or polymyxin B, it will markedly reduce intestinal flora.

Neomycin

Neomycin is a potent antibiotic obtained from cultures of *Streptomyces fradiae*. It is bactericidal and highly effective against a wide variety of bacteria, both gram-negative and gram-positive. It is particularly effective in treatment of infections due to *K. pneumoniae*, *H. influenzae*, *Pseudomonas* and *Proteus*. Microorganisms do not readily develop resistance to neomycin. It is extremely stable and not inactivated by exudates, enzymes or products of bacterial growth. Unfortunately, it has caused deafness and renal damage when it has been given in too high doses or for too long a period of time.

Intramuscular use—Intramuscular administration of neomycin is limited to treatment of severe systemic infections.

Preparation of solution—Neomycin sulfate is supplied in vials containing 0.5 gm. Adding 2.5 ml. of sterile isotonic solution of sodium chloride to a vial results in a solution containing 200 mg. per milliliter. The prepared solution should be used within 24 hours. Discard portions remaining thereafter, even though there is a considerable waste of material in therapy of small children.

Dosage—See table 1. The total daily dose should never exceed 1 gm., and the duration of therapy should not exceed 10 days.

Warning—If therapy is prolonged beyond 10 days and the total dosage exceeds 7 mg. per pound of body weight per day, signs of toxicity to renal and auditory functions are likely. The toxic effects of neomycin on the eighth nerve are principally auditory, are additive to those previously produced by streptomycin therapy, if any, and are irreversible. Nephrotoxic manifestations include mild albuminuria, granular casts, oliguria and elevated blood urea nitrogen. All the urinary findings disappear when the drug is discontinued, and their appearance during therapy does not contraindicate continued use unless intrinsic renal disease requires termination.

Precautions—1. If renal function is impaired, lower doses of neomycin are required because of impaired excretion of the drug and the resulting increase in serum concentration.

2. Deafness may result from therapy if renal function is decreased. Careful urinalysis and determination of nonprotein nitrogen or blood urea nitrogen should be done before therapy is instituted.

3. During therapy, urinalysis should be done daily and blood urea nitrogen determinations repeated every four days.

4. Audiometric tests are advisable before and during the course of therapy, especially in patients who have received streptomycin or dihydrostreptomycin previously.

5. In any case, therapy should not be continued longer than 10 days and the total daily dosage should not exceed 1 gm.

Oral administration—Neomycin is of singular value for rapid suppression of bacterial growth in abdominal surgery or other instances when complete eradication of bacterial flora of the bowel is desired. The drug is poorly absorbed from the gastrointestinal tract and will not cause systemic toxicity unless the mucosal lining is impaired, as in ulcerative colitis. Polymyxin given simultaneously improves effectiveness.

Dosage—Routine dosage is given in table 1. For rapid sterilization of bowel preoperatively, 50 mg. per pound of weight per day is usually given for three doses, one hour apart, and followed by administration every four to six hours.

Caution—1. Administration of neomycin to premature infants or to patients with ulcerative colitis or other abnormality of the intestinal mucosa may result in systemic absorption and toxicity.

2. Overgrowth of yeasts may follow eradication of normal bowel flora, as with other broad-spectrum antibiotic therapy. However, recent evidence suggests that the presence of yeasts in massive amounts is not of pathologic significance in itself and may occur in the absence as well as in the presence of diarrhea. Conversely, prevention of such overgrowth of yeasts by the use of nystatin does not in any way change the incidence of postantibiotic diarrhea.

Erythromycin, Novobiocin and Ristocetin

Erythromycin, novobiocin and ristocetin are particularly useful against staphylococci and other gram-positive organisms.

Erythromycin—Erythromycin is extremely useful in therapy of infections due to gram-positive organisms, particularly the penicillin-resistant staphylococci commonly encountered in nursery epidemics and hospital superinfections. It should generally be used in combinations with other effective agents, because resistance develops quickly in the therapy of staphylococcic and enterococcic infection.

There is significant cross resistance to oleandomycin, which, however, is a much weaker agent. Therefore, in order to give erythromycin the best chance in hospital and office ther-

apy, the use of oleandomycin should be strongly discouraged, as it has no advantages over erythromycin and is much less effective when used alone.

Indications for use—Erythromycin is indicated in treatment of infections due to penicillin-resistant, erythromycin-sensitive bacteria and also is of use in treatment of persons sensitive to penicillin. It is the agent of choice in treatment of patients with diphtheria or of diphtheria carriers. It should be included in combination with other agents such as bacitracin, chloramphenicol and streptomycin in the treatment of penicillin-resistant staphylococcic infections. Erythromycin is probably of use in the prevention of rheumatic fever as an alternative to penicillin. In combinations with bacitracin or streptomycin it may be employed in treating alpha streptococcal endocarditis.

Dosage—See table 1. Oral medication is readily absorbed and is preferred. When it is necessary to resort to parenteral administration, the intravenous route is preferable.

Novobiocin (Albamycin, Cathomycin)—Novobiocin is a bacteriostatic agent which is highly active against a wide variety of staphylococci. It is also effective against several strains of *Proteus* and thus becomes of considerable importance in therapy of infections caused by this pathogen. The activity of novobiocin is increased by an acid medium, and it may therefore be desirable to acidify the urine in the treatment of urinary tract infections due to novobiocin-susceptible organisms, such as *Proteus* and staphylococci. Novobiocin does diffuse into the pleural and ascitic fluid, but in general does not appear in significant concentration in the cerebrospinal fluid unless very large doses are used and marked inflammation of the meninges exists. Novobiocin is concentrated in the liver and excreted in the feces and urine.

Dosage and route of administration—See table 1. Oral administration is recommended for general use. Intramuscular use should be discouraged in small children because of the high incidence of local reactions. The intravenous route is generally preferable. However, if intramuscular use is necessary, any calculated portion of the 5 cc. solution, containing 500 mg. of novobiocin, may be injected in a 1:2 dilution with saline if given deep into the gluteal muscle. It is generally better to divide the dose and administer it at two injection sites, and the injection sites must be rotated according to plan.

For intravenous use it must be noted that solutions containing dextrose are incompatible with novobiocin and should not be used. In general the 5 cc. concentrated solution may be diluted from 30 to 100 cc. with sterile sodium chloride and administered by intravenous infusion slowly over a period of 20 to 30 minutes.

Toxic effects—See table 3. In at least 35 per cent of all children, intense sensitization to novobiocin will develop. Urticaria, eosinophilia and a striking maculopapular dermatitis are common. A few instances of leukopenia also have been observed. In general, these toxic effects disappear rapidly when the drug is discontinued. Allergic reactions may be modified in part by antihistaminic agents.

In a number of patients, a yellow pigment has been found in the plasma which probably is a metabolic by-product of the drug. This pigment may interfere with determination of bilirubin and icteric index, even though it is not associated with abnormal liver function tests or liver enlargement. To differentiate bilirubin and the metabolic pigment of novobiocin, the plasma is washed with chloroform. A bilirubin determination of the washed plasma will give a normal result if the pigment is a novobiocin metabolite, while in the presence of true jaundice only a slight change in bilirubin values will occur.

The very high incidence of side reactions makes it desirable to restrict the use of novobiocin to therapy of infections difficult to treat with other, less sensitizing drugs, such as penicillin. For example, in treatment of beta streptococcal infection, *Neisseria* infections, and so on, penicillin is much preferred to novobiocin. On the other hand, in therapy of resistant *Proteus* and staphylococcic infections, novobiocin has been shown to be extremely effective. In therapy of staphylococcic infections, combination with erythromycin, bacitracin or ristocetin may be advisable.

Ristocetin (Spontin)—The unique feature

of ristocetin therapy is that at present its use is restricted to the intravenous route. Its spectrum is similar to that of erythromycin and novobiocin. There is no cross resistance to other known antibiotics, and the agent is bactericidal at about the same concentration at which it is bacteriostatic. Ristocetin is indicated for treatment of infections caused by penicillin-resistant staphylococci which justify the use of intravenous therapy. It may be used in combination with other effective agents, such as novobiocin, erythromycin or bacitracin.

Dosage and route of administration—See table 1. Ristocetin is administered by the drip technic. The required dosage is dissolved in 5 per cent dextrose in water and is administered in 35 to 40 minutes. For 250 mg. of ristocetin, 125 ml. of solution is recommended; for 500 mg., 250 ml. of solution will be required; but 1 to 2 gm. of ristocetin may be administered in a single group infusion of 500 ml. of 5 per cent dextrose in water. The maximal concentration recommended for intravenous administration is 1.25 per cent, and the maximal rate of administration is 2 cc. per minute of the 1.25 per cent concentration. Sterile solutions of ristocetin may be stored for one month in the refrigerator without significant loss of potency.

Combinations of Antibiotics

As already stated, there are at least 69 preparations providing fixed combinations of two, three, four or five antibiotics. Commercial exploitation of the physician's fear regarding the emergence of resistance, or doubt of his own diagnostic capabilities, has resulted in much needless and sometimes dangerous multiple antibiotic therapy. Fixed combinations are particularly undesirable in the pediatric age group, as judged by the fact that many of them are not particularly suited for pediatric therapy. For example, a fixed combination of penicillin and streptomycin, such as COMBIOTIC®, results in streptomycin dosage which is too high and a penicillin dosage which is too low for optimal therapy of children. When combinations are desired, the physician is quite able to provide for them in his own way and based on his own judgment.

In many instances, fixed combinations and multiple drugs thrown together reflect the competitive nature of the drug business rather than true therapeutic indication or need. You will recall the advertising campaigns for stress-fortified, vitamin-loaded antibiotic medication, which has since pretty well disappeared only to be succeeded by attempts to increase absorption and blood levels, each accompanied by high-pressure publicity campaigns. These "advances" might better be considered advertising gimmicks in a highly competitive business rather than good medicine for treating sick children.

Combinations of antimicrobial agents may be rationally administered for the following reasons.

1. Mixed infection.
2. Prevention of emergence of resistant bacterial mutants, for example, use of streptomycin plus isoniazid, or erythromycin plus penicillin.
3. Additive or synergistic effects against homogeneous population of relatively resistant organisms.

The drug treatment should be continued for an adequate time to insure complete eradication of all infection. Antibiotic therapy should be continued for at least four days in the face of prompt clinical response if its use was indicated in the first place. On the other side of the scale, therapy for many months may be necessary for difficult chronic infections of bone, kidney or skin.

Long-term Antibiotic Prophylaxis

Long-term antibiotic prophylaxis is clearly indicated for children who have had a clinical diagnosis of rheumatic fever or poststreptococcal glomerulonephritis. It has been clearly shown that therapy with penicillin, 200,000 units twice a day or long-acting preparations in a dosage of 1,200,000 units given once a month, prevents reinfection with the beta streptococci and recurrences of these life-threatening diseases. If one considers the shortening of life span by repeated attacks of rheumatic fever, there should never be any doubt as to the physician's responsibility for maintenance of lifelong antibiotic prophylaxis.

TABLE 4

TUBE SENSITIVITY TESTS* OF PATHOGENIC STAPHYLOCOCCI TO NINE ANTIBIOTICS

	PENICILLIN	BACITRACIN	STREPTOMYCIN	CHLORAMPHENICOL	TETRACYCLINE	ERYTHROMYCIN	NEOMYCIN	NOVOBIOCIN	RISTOCETIN
Resistant	49 (90%)	12 (22%)	43 (80%)	27 (50%)	38 (70%)	37 (69%)	24 (44%)	14 (26%)	9 (20%)
Slighly sensitive	4 (8%)	31 (58%)	5 (9%)	15 (28%)	8 (15%)	12 (22%)	16 (30%)	10 (19%)	23 (51%)
Highly sensitive	1 (2%)	11 (20%)	6 (11%)	12 (22%)	8 (15%)	5 (9%)	14 (26%)	30 (55%)	13 (29%)
TOTAL	54	54	54	54	54	54	54	54	45

*For a description of the tube sensitivity test, see the article by Jawetz and associates.[2]

In one of our recent surveys, however, we found that only 35 per cent of children with diagnosed rheumatic fever who had been started on prophylactic therapy were still receiving penicillin one year later. In the same vein, in cases of children with fibrocystic disease, dysgammaglobulinemia and other chronic debilitating diseases characterized by frequent bacterial infections, long-term use of daily tetracycline prophylaxis would certainly be indicated. Finally, children who receive steroid therapy, regardless of whether it is for a short or for a long period, should always be on antibiotic prophylaxis because of the markedly increased risk of generalized bacterial complications in children receiving cortisone or related compounds.

Sensitivity of Hospital Staphylococci to Various Antibiotics

The susceptibility of hospital staphylococci to various antibiotics is in a constant state of flux. Local custom of antibiotic use has much to do with the percentage of strains isolated that are resistant to a given agent. In general, it has been observed that the majority of pathogenic hospital staphylococci are penicillin-resistant. A surprising and increasing number are resistant to other antibiotics as well. Table 4 is an analysis of 54 pathogenic strains whose sensitivity was determined by the tube method against penicillin, bacitracin, streptomycin, chloramphenicol, tetracycline, erythromycin, neomycin, novobiocin and ristocetin.[2] Table 5 shows 29 combinations of possible antibiotics and the relative effectiveness. These data, obtained at the University of Colorado Medical Center in 1957, reveal that highly effective therapy, even with combinations, is not too likely in the usual dosages and that frequently one must settle for any combination that proves even moderately sensitive by in vitro tests.

Tables 4 and 5 point the way which previously was suggested by the experience of Lepper and associates,[3] who showed that exclusive use of erythromycin in a Chicago hospital, as a substitute for penicillin, over a six month period resulted in increased usefulness of penicillin in the treatment of staphylococcic infec-

TABLE 5

TUBE SENSITIVITY TESTS OF PATHOGENIC STAPHYLOCOCCI TO TWENTY-NINE COMBINATIONS OF ANTIBIOTICS

	RESISTANT	SLIGHTLY SENSITIVE	HIGHLY SENSITIVE	TOTAL NUMBER
Penicillin and streptomycin	44 (81%)	7 (13%)	3 (6%)	54
Penicillin and bacitracin	31 (58%)	17 (31%)	6 (11%)	54
Bacitracin and streptomycin	33 (61%)	15 (28%)	6 (11%)	54
Penicillin and tetracycline	35 (65%)	14 (26%)	5 (9%)	54
Penicillin and chloramphenicol	38 (70%)	12 (22%)	4 (8%)	54
Penicillin and erythromycin	39 (72%)	13 (24%)	2 (4%)	54
Streptomycin and tetracycline	38 (70%)	12 (22%)	4 (8%)	54
Streptomycin and chloramphenicol	44 (81%)	7 (13%)	3 (6%)	54
Streptomycin and erythromycin	45 (83%)	5 (9%)	4 (7%)	54
Bacitracin and tetracycline	24 (44%)	15 (28%)	15 (28%)	54
Bacitracin and chloramphenicol	22 (40%)	16 (30%)	16 (30%)	54
Bacitracin and erythromycin	24 (44%)	16 (30%)	14 (26%)	54
Neomycin and penicillin	21 (39%)	25 (46%)	8 (15%)	54
Neomycin and streptomycin	38 (70%)	8 (15%)	8 (15%)	54
Neomycin and bacitracin	13 (24%)	22 (41%)	19 (35%)	54
Neomycin and chloramphenicol	43 (80%)	4 (7%)	7 (13%)	54
Neomycin and tetracycline	27 (50%)	15 (28%)	12 (22%)	54
Neomycin and erythromycin	33 (61%)	13 (24%)	8 (15%)	54
Neomycin and penicillin	14 (26%)	21 (39%)	19 (35%)	54
Novobiocin and bacitracin	4 (7%)	19 (35%)	31 (58%)	54
Novobiocin and tetracycline	10 (19%)	14 (26%)	30 (55%)	54
Novobiocin and erythromycin	21 (40%)	17 (31%)	16 (29%)	54
Novobiocin and neomycin	8 (15%)	16 (30%)	30 (55%)	54
Ristocetin and penicillin	18 (40%)	14 (31%)	13 (29%)	45
Ristocetin and bacitracin	10 (22%)	17 (38%)	18 (40%)	45
Ristocetin and tetracycline	13 (29%)	14 (31%)	18 (40%)	45
Ristocetin and erythromycin	13 (29%)	21 (46%)	11 (25%)	45
Ristocetin and neomycin	6 (13%)	23 (51%)	16 (36%)	45
Ristocetin and novobiocin	5 (11%)	15 (33%)	25 (56%)	45

tions which previously had been almost universally penicillin-resistant, while erythromycin resistance among hospital organisms rose from 0 to 75 per cent. When erythromycin was discontinued for six months and penicillin was reintroduced, the percentage of penicillin-resistant strains rose from 38 to 95 per cent while erythromycin-resistant strains dropped from 75 to 32 per cent.

Perhaps another example is the decrease in the use of chloramphenicol which followed the discovery of hematologic complications caused by this agent and the subsequent increasing usefulness of the drug in antistaphylococcic therapy. As physicians have now fairly well forgotten about chloramphenicol toxicity, its use has increased tremendously and its usefulness thereby has proportionately decreased.

The indication is clear that hospital boards may themselves decide to restrict the use of one or more potent antistaphylococcic agents in an effort to retain an "ace in the hole" if a difficult therapeutic problem should arise. Chloramphenicol, novobiocin and ristocetin might well be restricted voluntarily in order to reserve them for situations in which they are absolutely needed.

Summary

Happily, medicine remains a highly individualized vocation. What is more fitting, therefore, than that each of us should work out his own therapeutic philosophy? It is our hope that this philosophy will be at once enlightened and responsible.

A rational approach to the selection of the proper antimicrobial agent in treatment of children with bacterial disease requires some basic information and a considerable degree of sales resistance to undue or premature ad-

vertising claims. It is suggested that the pediatrician formulate a tentative specific etiologic diagnosis when faced with an illness, a diagnosis usually based on clinical impression and occasionally made by employing the help of bacteriologic study *prior* to the administration of the antibiotic drug, and that he give such a drug only when it is indicated. A good rule in therapy appears to be to give a large enough amount of the drug to which the etiologic microorganisms are susceptible by the proper route and as early as possible, and to continue such treatment for an adequate time to insure eradication of the infection.

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1958

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 10-13 Municipal Auditorium Cleveland, Ohio

Special Considerations Regarding Fractures in Children

The treatment of fractures in children presents problems that are in certain instances quite different from similar fractures in adults. Factors of importance are the difference in physiologic response to trauma of active growing bone as compared with mature, relatively static bone; the effect of trauma on epiphysial growth; and the relative scarring with contracture of muscles and joint capsule following trauma in a child as compared with an adult. Examples will be cited, and the effect of these physiologic differences on treatment will be stressed.

CHARLES H. HERNDON, M.D.

Associate Professor of Orthopedic Surgery, Western Reserve University School of Medicine, Cleveland

Nonoperative Treatment of Cervical Carcinoma

HERBERT E. SCHMITZ*

Stritch School of Medicine of Loyola University, Chicago

HERBERT E. SCHMITZ

LAST evening I had dinner with about a dozen physicians from Chicago, and various subjects were discussed. One of our confreres said to the group, "Have you noticed that the incidence of carcinoma of the cervix is lessening?" Everyone replied he had not. "Well," he said, "we made a study of it in our hospital, based on the number of patients with cancer and the hospital days, and there is a definite decline." We began to discuss the reason for this, and everyone pretty well agreed that routine cytologic testing or screening of patients was the responsible factor. To substantiate this point it was shown that larger numbers of patients are being admitted to the hospital with a diagnosis of carcinoma in situ or preinvasive cancer. If that is so, we have the first proof that screening of patients eventually will decrease the number of cases of invasive cervical cancer. For if we successfully treat preinvasive cancer we prevent invasion from beginning.

Screening studies have been carried out in various parts of the United States, and we know that the accuracy of the cytologic smear in detecting cervical cancer is about 95 per cent when the technic is meticulous. It seems inevitable that we will eventually accomplish what appears to be the trend at this time.

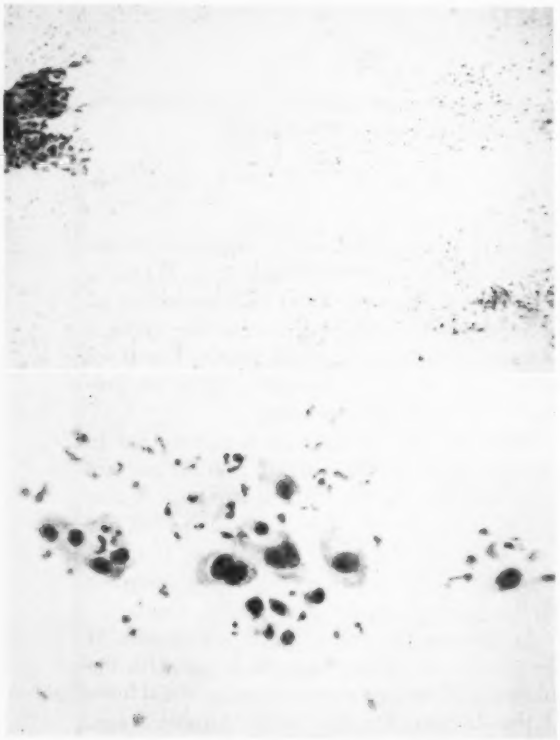
To discuss the treatment of carcinoma of the cervix, therefore, we must begin with the diagnosis of the preinvasive or preclinical form of the disease; for this is the curable stage. We must also have a clear visualization of the extent of the disease. For this reason, Henry Schmitz of our clinic introduced the first clinical grouping of cancer invading the cervix. The Schmitz group I includes lesions from a microcancer, the earliest sign of invasion, to a lesion, exophytic or endophytic, not larger

*Professor of Obstetrics and Gynecology, Stritch School of Medicine of Loyola University, Chicago, Illinois.

Presented before the forty-second annual Assembly of the Interstate Postgraduate Medical Association at Chicago.

FIGURE 1. Equipment for making a cytologic smear of the cervix.

FIGURE 2. Technic of staining the slide after it is fixed.



FIGURES 3 and 4. Low-power and high-power photomicrographs of a cytologic smear illustrating typical cancer cells.

than 1 cm. in circumference. This is a more rational stage I than that in the International classification. Cancer involving the entire cervix is not an early stage; in 20 per cent of instances of International stage I there are complicating pelvic lymph nodes carrying cancer cells, and that means the patient is almost 95 per cent incurable.

The International classification of clinical cancer carries a stage O to designate the preinvasive or in situ lesions. However, stage I includes all cases from those in which there is microscopic evidence of invasion to those involving the entire cervix.

Just a few years back, all of us were taught in medical school and were teaching our students that the earliest symptom of cancer of the cervix was discharge, that the most alarming was bleeding and the most disappointing was pain. Today we teach that early cancer of the cervix does not produce symptoms and that it is present in the preinvasive form for an indefinite number of years (the average appears to be about eight). Therefore it is going to be possible for us to detect this preinvasive lesion before invasion begins.

Figure 1 depicts the equipment for making a cytologic smear. This should be on your examining table at all times. It consists of a glass slide with the name and case number, an identification card, a paddle for taking the smear, a bottle of fixative—95 per cent alcohol and ether—a speculum and light. Figure 2 shows the technic of staining the slide after it is fixed. We use the regular Papanicolaou stain. Figures 3 and 4 are low-power and high-

FIGURE 5. Four quadrant biopsy of the cervix.

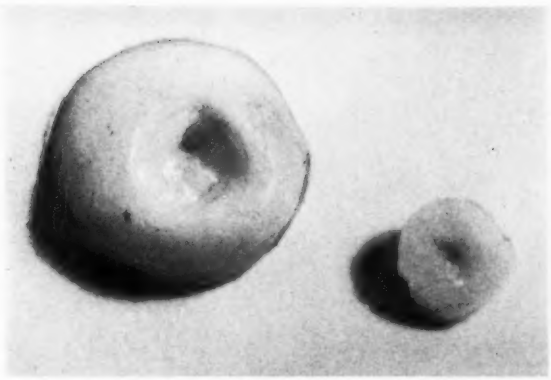


FIGURE 6. Cold conization of the cervix.

power photomicrographs of a smear which illustrate how clearly tumor cells stand out. The clumps of cells with large, irregular, deep-staining, vacuolated nuclei are typical of cancer cells. We find these cells simply by making routine smears in supposedly well patients, patients without any evidence of disease or of malformation or erosion of the cervix.

When such cells are found and the smear is reported as suspicious (class III) or showing definite cells (class IV) or unquestionable cancer tissue (class V), *it is a challenge* to us to find the location of the carcinoma somewhere in the genital tract.

There are those who maintain that the smear is more accurate than the biopsy, and they base that belief on the fact that they have obtained a positive smear and have been unable to demonstrate the primary site until they removed the uterus, cut it into blocks and random-sectioned the blocks. For example, John Brewer reported a case of carcinoma of the pancreas in which the patient had few symptoms of disease. She had a breakthrough of cells to the peritoneum; tumor cells desquamated downward into the peritoneal fluid and were washed through the fallopian tubes, and a positive smear was obtained from the vaginal pool. Exploration was performed because the carcinoma could not be found, and examination of the upper part of the abdomen demonstrated an early carcinoma of the pancreas with an implant on the peritoneum.

Ovarian and tubular malignancies have been diagnosed by means of the cytologic smear, but that does not mean that it is more accurate than biopsy. It means that the occasional abnormal location is going to be divulged, and it is for us to find it when a positive smear has been obtained. Most everyone, including Papanicolaou, agrees that the smear is not sufficient evidence to warrant instituting definitive therapy. A biopsy must be taken to provide pathologic corroboration of the diagnosis of in situ or invasive cancer.

To find the lesion, we have to biopsy, there is no question about that. No one is going to carry out definitive treatment until he has determined whether or not he can locate the lesion in this manner. We advocate a four quadrant biopsy as shown in figure 5.

The cervix may appear to be a normal nulliparous cervix, because these lesions originate in the endocervix at the squamocolumnar junction and grow upward against the least resistance, which is against the single-layered columnar epithelium. Therefore they are not visible for long periods; the ulceration or nodularity that eventually appears on the portio of the cervix does not represent an early stage of cancer.

The four quadrant biopsy should be generous. Pieces of tissue should be taken from points corresponding to the clock numerals 12, 3, 6 and 9. If these pieces show carcinoma in situ, either you have to go back and take

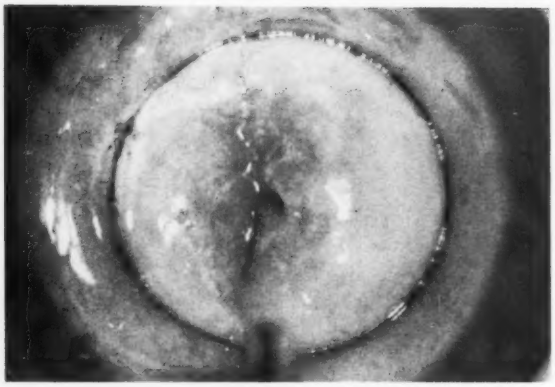


FIGURE 7. Cervix in the fourth month of pregnancy. The mucoid discharge and slight ectropion are not unusual in pregnancy, but a Papanicolaou smear was positive.

further biopsies in between those points, or you have to cone. We prefer coning.

Figure 6 shows a cold conization of the cervix. This is best done with a Bard-Parker bistoury. As you see, it removes the entire squamocolumnar junction and permits you to open the flap. If you cut that into 14 little blocks, and sample each block by one or two or three sections, you are not going to overlook the lesion.

Figure 7 illustrates the cervix of a woman in the fourth month of pregnancy. The usual mucoid discharge is visible. The mucus is coming from the cervical os. There is a little protrusion or ectropion, which is not unusual in pregnancy, and still this woman had a positive Papanicolaou smear. We have begun making smears in all prenatal patients, because we find carcinoma in situ in the twenties and the thirties. If we cone these patients and the smears become negative, we permit them to go on to normal delivery. We have not hesitated to cone a cervix up to the thirty-sixth week of pregnancy.

Figure 8 illustrates one of the conditions that sometimes confuse us, especially when we have a grade III smear. A grade III smear indicates a suspicious lesion. There are no cells that appear definitely malignant, but they are abnormal, and the question is, are there malignant cells about? In this instance you see a good deal of activity around the basal membrane, and this is what we call basal cell hyperactivity. It is a response of normal tissue to some type of insult, inflammation or injury. Under high power one sees marked activity, but there is no loss of stratification and the upper layers of the epithelium are easily differentiated. At times an inexperienced pathologist may call this carcinoma in situ, but it is never carcinoma in situ when there is lack of penetration of all the cell layers.

Figure 9 depicts another situation that often confuses us and confuses pathologists, that is, the process of healing, so-called epidermoidization. The squamous epithelium pushes back and replaces the normal low columnar epithelium within the gland, and when certain sections are taken through the gland and squamous cells are found at the depth of the glands there may be confusion for fear there has been penetration or extension of a squamous cell lesion.

Figure 10 illustrates what we mean by carcinoma in situ. Irregularity and atypia begin in the lower area of the basal layer of the squamous epithelium. There is a change in the polarity of the cells; you see them coming upward and beginning to diverge and go off in different directions. This penetrates through the outer layers causing complete replacement with this type of cell. The basal membrane is intact; therefore this cannot be called invasive carcinoma, although this is quite evident in this section. Very frequently the diagnosis is difficult.

I should like to describe a few typical examples of what the proper approach can accomplish when a patient presents herself for examination and when she has a general physical examination including cytologic study of the cervix. There are enough laboratories and enough mailing containers so that cytology is available to all physicians, no matter what part of the country they live in.

A 41 year old white woman, Para II, first noted postcoital spotting in April 1955. Menses were normal. The first medical consultation was in June 1955. A 2 cm. lesion was noted on the anterior lip of the cervix, a very superficial lesion. Papanicolaou smear showed it to be group V, which is positive for squa-

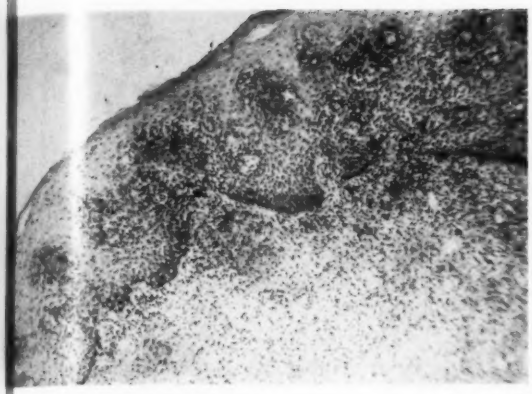


FIGURE 8. Basal cell hyperactivity. Cells do not appear definitely malignant, but they are abnormal.

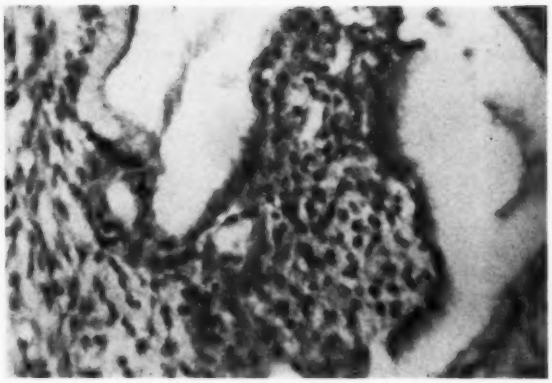


FIGURE 9. Epidermoidization. Confusion may arise when squamous cells are found at the depth of the glands.

mous cell carcinoma. The pathologist reported carcinoma of the cervix, clinical group II or stage I. I doubt that we would have recognized this as clinical carcinoma if our suspicion had not been aroused by the findings of cytologic study. Biopsy confirmed the diagnosis. Figure 11 shows the smear. You see atypical cells under high power. There is no question about those being tumor cells in a clump of tissue. Figure 12 is a photomicrograph of the tissue. There is no question about this being invasive carcinoma.

A 37 year old woman, Gravida IV, Para II, had a routine Papanicolaou smear in the prenatal clinic on June 8, 1955. Her last menstrual period had occurred on December 25, 1954, and her expected day of confinement was October 2, 1955. The smear showed group III cells—suspicious, not positive. The cervix appeared eroded about the external os. A biopsy showed carcinoma in situ of the cervix. Figure 13 is a photograph of the lesion. There is nothing much to arouse suspicion; the mucus associated with pregnancy is visible, but there appears to be a smooth, glistening covering of squamous epithelium.

A 36 year old woman, Gravida IV, Para III, had a routine Papanicolaou smear in the prenatal clinic on March 23, 1955. Her last menstrual period had occurred in October 1954 and her expected date of confinement was August 1, 1955. The smear was classed as

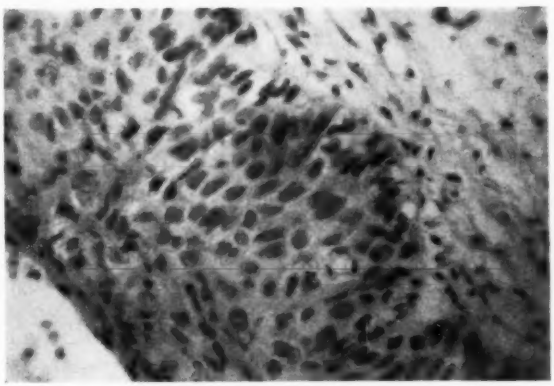


FIGURE 10. Carcinoma in situ.

group IV. The cervix appeared eroded about the external os. A biopsy revealed invasive squamous cell carcinoma of the cervix.

We accept anyone with a background of two years of science and train them in our laboratory to be cytotechnicians or so-called screeners. After six months they will screen smears with a high degree of accuracy.

What is the result of the finding of carcinoma in the in situ or preinvasive stage? Are the efforts worthwhile? That is what I implied when I said that there are going to be fewer patients with carcinoma of the cervix. In carcinoma in situ, conization or superficial amputation removes the lesion. Follow-up smears have indicated that there is no residual. If the

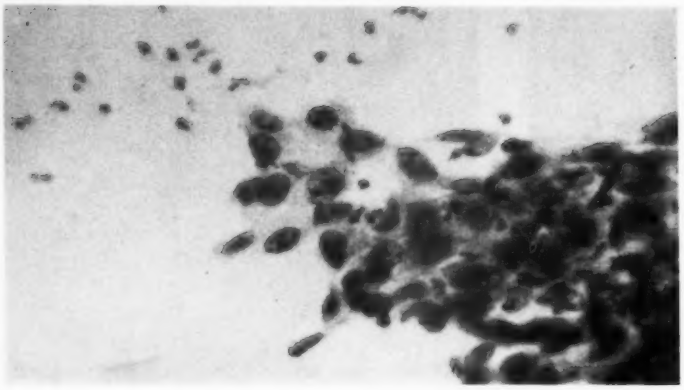


FIGURE 11. High-power view of cytologic smear shows typical tumor cells. Patient complained of postcoital spotting, and a superficial 2 cm. lesion was noted on the anterior cervical lip. Biopsy confirmed the diagnosis.

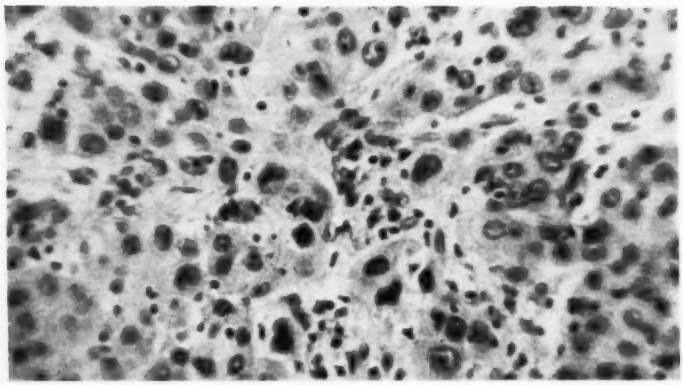


FIGURE 12. Photomicrograph of the tissue.

smears continue to be positive or if the lesion recurs later on, then it is time to remove the uterus because you have not removed all the disease with the cone biopsy. That is the surgical treatment—mostly in prevention. But remember this: Even with conization and multiple biopsy, in cases in which the diagnosis of carcinoma in situ has been made, about 30 per cent in our clinic have shown invasive tendencies or breakthrough on complete serial section of the cervix.

Over a 17 year period, 340 patients with cancer of the cervix were admitted to our clinic. Analysis of these 340 cases is shown in the top portion of table 1, which separates them according to the four clinical groups of the Schmitz classification. The latter divides the stage I lesions into groups I and II. In the 340 cases there is an over-all salvage rate of 44.4 per cent. These patients were treated with x-ray and radium.

The first fact to realize is that the possibility of overcoming the disease is eight times greater when the lesion is in group I than when it is in group IV. How long does it take to progress from I to IV? We do not know. In some instances it takes only a few months.

Why do we treat these patients with irradiation and not surgically, as has been adopted again in some clinics? Because there are no published statistics of any group of cases treated surgically that show an advantage over irradiation therapy. If we analyze all the cases reported in a series, we find that the survivals are in the Schmitz stages I and II, where there are very few nodal invasions. When the disease has extended into the nodes, the surgical advocates tell us that one must employ sur-

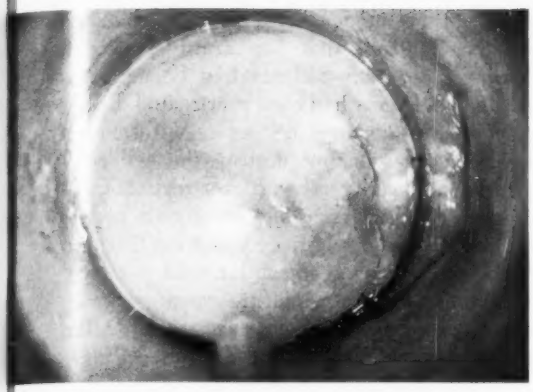


FIGURE 13. Carcinoma in situ of the cervix. Patient had a routine Papanicolaou smear in the prenatal clinic, and it showed suspicious cells. Biopsy demonstrated preinvasive cervical cancer.

TABLE 1

END RESULTS IN CARCINOMA OF THE CERVIX

CLINICAL GROUP*	NUMBER OF CASES	SURVIVAL	
		Number	*Per Cent*
Primary cases,† 1933-1950			
I	37	32	86.5
II	82	53	64.6
III	141	58	41.1
IV	80	8	10.0
TOTAL	340	151	44.4
Secondary cases,† 1946-1950			
I	5	2	40.0
II	15	10	66.6
III	22	9	40.9
IV	46	3	6.5
TOTAL	88	24	27.2

*Schmitz classification.

†Primary cases are those in which the diagnosis was first made in our clinic, and treatment was instituted and carried through there; secondary cases are those in which the patients had been treated unsuccessfully elsewhere and came for further irradiation therapy.

gery because the disease in the nodes is resistant to irradiation therapy. That has been disproved. Meigs, who reintroduced the surgical procedure, has admitted that it is an erroneous statement. He tells us that in his own experience in studying the sensitivity and resistance of tumors by the Graham method, he finds that many of the so-called resistant tumors—resistant to irradiation—can be cured, or arrested, by irradiation therapy. So at the present time there is no criterion for sensitivity or resistance. We prefer to treat all the patients with irradiation therapy, and then follow with cytologic study at frequent intervals.

If the findings of cytologic study again become suspicious, then we rebiopsy, either by conization or by a four quadrant biopsy or endocervical curettage. If we find remaining active disease, we resort to the surgical eradication of the uterus and pelvic lymph nodes, because then there is nothing else to offer the patient. If you offer the patient combined irradiation and surgery routinely, you will then offer three patients out of every four an operative procedure they do not need, because there will be only one additional survival because of the surgical procedure. You have not the right to jeopardize the patient with an incidence of 12 per cent fistulas or 30 per cent complications, the incidence when surgery is used in previously irradiated patients. The incidence would be only 11 per cent in primarily irradiated patients. We have stayed with irradiation therapy. We have no evidence that anyone else with surgical procedures has improved or surpassed these end results. We are, at the same time, taking care by irradiation of the group III and group IV cases which are not surgical—unless you wish to resort to the so-called all-American or exenteration procedure.

In cases of irradiation failure we have used radical surgical procedures in 120 patients. We have a 42 per cent five year survival. We have a 68 per cent two year survival, and I will say that those patients have a smoother exodus than they would have if they had not had the operative procedure—but that is for another discussion.

The lower part of table 1 demonstrates what happens when a patient has been treated unsuccessfully elsewhere and then comes to you for further irradiation therapy. The over-all survival drops to 27 per cent. These are what we call secondary cases. The group in the upper part of the table represents the primary patients, whose diagnosis was made in the clinic and who were treated by us. What does

that mean? It means that treatment of the disease requires either a very unusual combination within one individual or the teamwork of a pathologist, a radiologist, a gynecologist and very frequently a physicist. If there cannot be complete plotting of a tumoricidal dose, and if that cannot be given as a continuous treatment which takes anywhere from three to five weeks and is so planned that every bit of the tumor-bearing area is equally irradiated, then the end results will suffer.

Some few years ago we published a study of what we call haphazard irradiation therapy of carcinoma of the cervix. We showed that there was but 17 per cent five year survival in a group of 605 patients who came under the treatment and supervision of men well qualified as gynecologists but without the bilateral training of radiation therapy or the assistance of a tumor team with the radiation administered by radiologists. In other words, today we can have radium sent to us with instructions on how to apply it. The man who sends us the radium has not seen the patient and knows nothing about the measurements of the patient, and so on. We know that absorption curves, intensity of irradiation, and depth and extent of the tumor all enter into this plan, so we have to call that haphazard treatment. Many of the 605 patients had been undertreated, and many had been overtreated. Either way, the results are the same. With undertreatment you do not destroy the cell sufficiently and it recovers; with overtreatment you destroy all the protective walling-off of the tumor, the tumor bed from which healing and fibrosis will occur to entrap the cells.

In those cases in which treatment was adequate according to present-day standards, the curability rose to the accepted levels.

In the secondary cases (table 1), the survival rate of patients with localized stage I lesions was only 40 per cent when it should have been 85 per cent or more. These failures were due to inadequate treatment. They become radioresistant, and that accounts for the failure. Therefore, in treating carcinoma we should have either a team or an individual specially trained in that treatment. But more important is the finding of the lesion before it is clinical, and then either preventing it in the premalignant stage or effecting a five year survival of at least 85 to 90 per cent in the early invasive stage.

1958

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 10-13 Municipal Auditorium Cleveland, Ohio

Practical Aspects of Anemia Therapy in Pregnancy

Anemia is a common complication of pregnancy. A background of information on iron metabolism will be presented, along with practical aspects of iron therapy. The discussion will include the use of oral and parenteral iron medication.

ROY G. HOLLY, M.D.

Professor and Head, Department of Obstetrics and Gynecology, University of Nebraska College of Medicine, Omaha

24 Hour Periodicity and Experimental Medicine

EXAMPLES AND INTERPRETATIONS

FRANZ HALBERG AND ROBERT B. HOWARD*

University of Minnesota Medical School, Minneapolis

THE term "periodicity analysis" is used to describe the analysis of physiologic changes along a 24 hour scale under conditions standardized to eliminate stimulation other than daily routine. This field of study has a long history and has been reviewed repeatedly.[1-5] We shall describe only briefly some clinical studies carried on at the University of Minnesota and at the Cambridge State School and Hospital with respect to a few selected periodic variables. For a discussion of these studies we shall rely on results of animal experiments at the same institutions. On the basis of the Minnesota work it will be suggested that periodicity analysis constitutes a useful investigative tool awaiting broader application. The sole purpose of this presentation is to stimulate interest in the field; the methodology[5] and important work by others[1-4] have been discussed elsewhere.

*University of Minnesota Medical School, Minneapolis; Cambridge State School and Hospital, Cambridge, Minnesota.

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FRANZ HALBERG

ROBERT B. HOWARD

Illustrative Examples

Unequal distribution of seizures in convulsive disorders—The unequal distribution of seizures during the hours of the day in certain patients with convulsive disorders has attracted attention since early clinical notes on the subject were published well over a century ago.[6-8] Figure 1 depicts the time distribution of epileptic seizures in a case observed for 20 years. Most of the seizures occurred during a limited fraction of the 24 hour period. Equally interesting, the time distribution of seizures

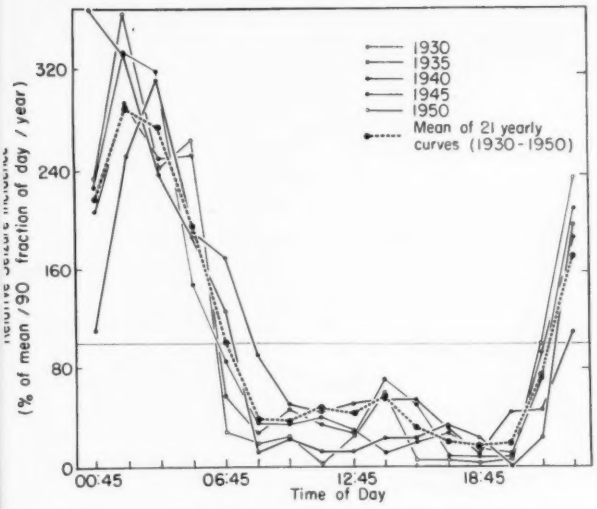

FIGURE 1. Unequal distribution of epileptic seizures during the hours of the day in a case observed for 20 years. "Night type."

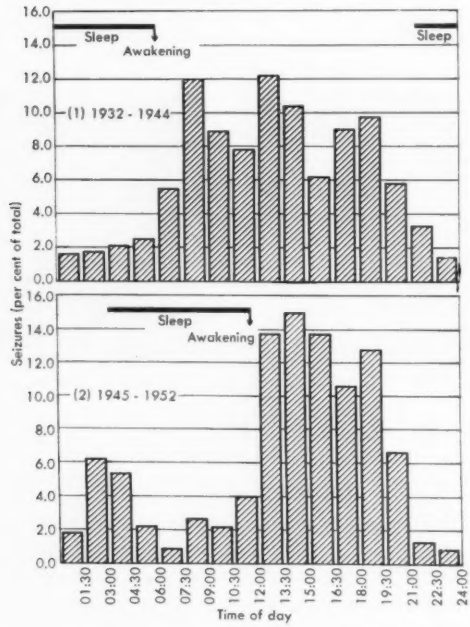

FIGURE 2. Unequal distribution of epileptic seizures during the hours of the day on two routines, maintained for many years. "Day type." Note change in seizure distribution following change in routine. Daily routine may be regarded as the environmental synchronizer of seizure rhythm; clock hour as such does not matter in determining times of occurrence of seizures.

remained remarkably consistent over a 20 year period. In the case of epilepsy represented in figure 2 a different seizure pattern is apparent. The latter figure shows, in addition, a shift in seizure distribution following a shift in routine.

A number of investigators have explored the possible factors underlying such periodic seizure types, and the pertinent literature has been reviewed.[4,9] More recently, one type of convulsive periodicity has become amenable to investigation in an appropriate experimental animal. The graph in figure 3 portrays the unequal incidence of convulsions in mice following exposure to audiogenic stimulation[10,11] (at opposite phases of daily eosinophil rhythm).

Periodic changes in blood—The 24 hour periodic changes in blood have been reviewed.[4,12,13] Figures 4 and 5 show 24 hour rhythms in eosinophil count and serum iron content, respectively. Profiles of these rhythms were determined under different circum-

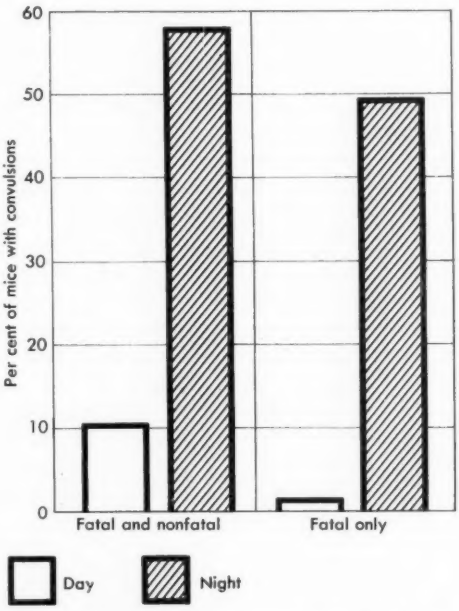

FIGURE 3. Unequal number of convulsions and of deaths from convulsions of comparable mice after exposure to identical auditory stimulation at different phases of eosinophil rhythm[10] (see figure 6).

stances, two on a regimen of four meals per 24 hours and a third on the usual three meals.

The three meals were of different caloric content, while the four meals were roughly isocaloric and equidistant (table 1). Of the two profiles on a four meal regimen, one was obtained with the subjects on their usual routine and in their usual environment, and the other was obtained in a constant-temperature room.[12] In the studies on the four meal regimen the medically normal subjects started on the diet either 48 or 12 to 24 hours before the first sampling, in a constant-temperature room and in their usual environment, respectively. Since venipuncture was done in each case every 90 minutes for 24 hours, all profiles are complicated by sampling effects, and those profiles determined under constant-temperature conditions are complicated by reactions to confinement as well. In other words the data show not only the rhythm studied but also what we do to determine it. Therefore, our definition of periodicity analysis, requiring the absence of stimulation other than daily routine, does not strictly apply, unless we qualify our stipulation with "as far as feasible."

It does seem certain, however, that the periodic changes recorded in figures 4 and 5 are not critically the result of repeated venipuncture. The major 24 hour trend stands out clearly, irrespective of start of study, which differed from case to case. Moreover, in animal experiments the effect of repeated venisection, though significantly demonstrable,[14] can be eliminated by using, at different times, separate groups of genetically and otherwise comparable mice.[15] Under such conditions the eosinophil rhythm, among others, stands out clearly, as may be seen in figure 6.

On the three regimens described previously, the timing of eosinophil rhythm was roughly comparable (figure 4), while that of serum iron content was not (figure 5). The latter changed on the four meal routine, apparently as a result of different factors involved in its synchronization with the environment.[12] It is interesting that in verified states of adrenocortical insufficiency the behavior of the two rhythms also differs; the eosinophil rhythm is obliterated[16-19] and that of serum iron content is not[12, 13] (figures 7 and 8).

Periodicity in a host-parasite relation—Figure 9 shows 24 hour periodicity in a host-parasite relation, a phenomenon known since 1879 when Manson[20] reported that the microfilariae of *Wuchereria bancrofti* make "a nightly appearance in the blood." An adrenal "inhibitor," $\triangle^1$-9α-fluorocortisol, was given

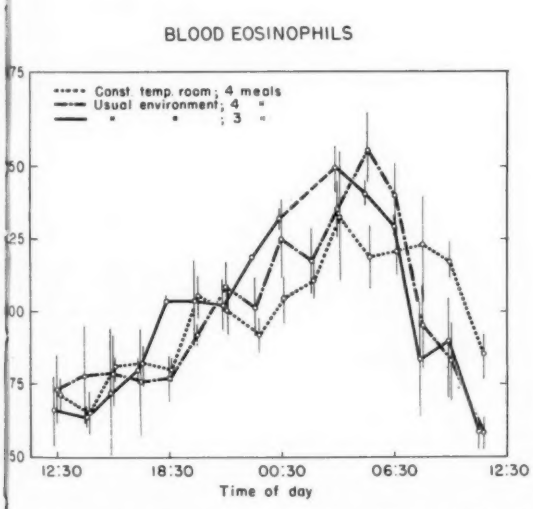

FIGURE 4. Comparable timing of eosinophil rhythm in man, on three different regimens (see text).

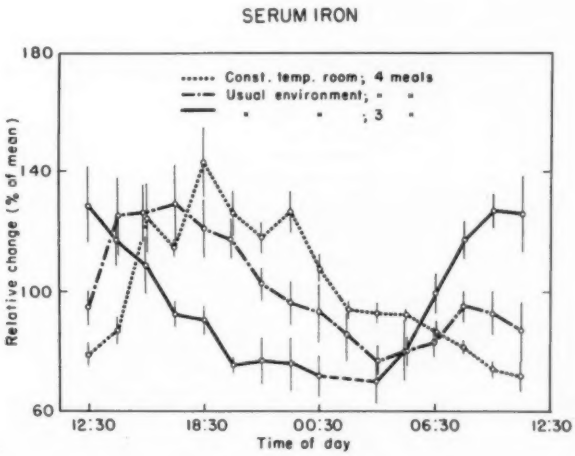

FIGURE 5. Different timing of serum iron rhythm in man, on three different regimens (see text).

TABLE 1

DIET USED IN STUDIES TO DETERMINE 24 HOUR RHYTHMS IN EOSINOPHIL COUNT AND SERUM IRON CONTENT

TIME	FOOD	GRAMS	CHO	PROTEIN	FAT	IRON (MG.)
0600	Bread	50	26.2	4.2	1.0	1.0
	Butter	25	0.1	0.15	20.2	0.05
	Corn flakes	10	8.6	0.77	0.03	0.16
	Milk, whole	240	11.8	8.4	9.4	0.17
	Sugar	4	4.0			0.7
	Cantaloupe	100	4.6	0.6	0.2	2.9
	Eggs	2	0.8	12.8	11.6	0.25
	Bacon	30	0.5	4.2	8.1	0.4
	Jam	20	14.2	0.1	0.06	0.09
	Coffee	150				
	TOTAL		70.8	31.22	50.59	5.72
1200	Bread	25	13.1	2.1	0.5	0.5
	Butter	10	0.04	0.06	8.1	0.02
	Milk, whole	240	11.8	8.4	9.4	0.17
	Mashed potato	100	20.7	3.1	6.6	0.5
	Fresh tomato	100	4.0	1.0	0.3	0.6
	Beef patty	100		19.2	23.6	2.8
	Jam	10	7.1	0.05	0.03	0.03
	Watermelon	100	6.9	0.5	0.2	0.2
	Sugar	6	7.0			
	Tea	150				
	TOTAL		70.64	34.41	48.73	4.82
1800	Bread	25	13.1	2.1	0.5	0.5
	Butter	25	0.1	0.15	20.2	0.05
	Milk, whole	240	11.8	8.4	9.4	0.17
	Jam	10	7.1	0.05	0.03	0.03
	Baked potato (no skin)	93	19.1	2.0	0.1	0.7
	Veal chop	100		19.2	4.0	2.9
	Lettuce	50	1.5	0.5	0.1	0.25
	Peaches (HOH) no juice	100	6.8	0.5	0.1	0.4
	Mayonnaise	21	0.6	0.3	16.3	0.09
	Sugar	10	10.0			
	Tea	250				
	TOTAL		70.1	33.20	50.73	5.09
0000	Bread	50	26.2	4.2	1.0	1.0
	Butter	20	0.08	0.12	16.2	0.03
	Milk, whole	240	11.8	8.4	9.4	0.17
	American cheese	20	0.3	4.8	6.5	0.1
	Pears in syrup (no juice)	100	18.4	0.2	0.1	0.2
	Cold beef	50		8.7	11.5	1.3
	Hard-cooked egg	1	0.4	6.4	5.8	1.4
	Jam	10	7.1	0.05	0.03	0.03
	Sugar	5	5.0			
	Tea or coffee					
	TOTAL		69.28	32.87	50.53	4.23

to three patients for a three day period.[21] Profiles of microfilarial and eosinophil counts were determined before and after administration of the compound. One possible effect apparent in figure 9 concerns the phase relations of rhythm in the group of three persons studied. The ascending and descending phases of microfilarial rhythms were more closely syn-

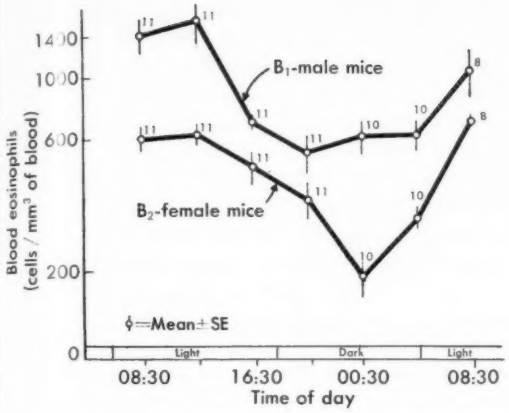

FIGURE 6. Eosinophil rhythm in male and female mice. Statistically, differentiation between sexes seems feasible with standardized periodicity analysis of eosinophil variation (justly regarded as "all too variable" when done without periodicity analysis).

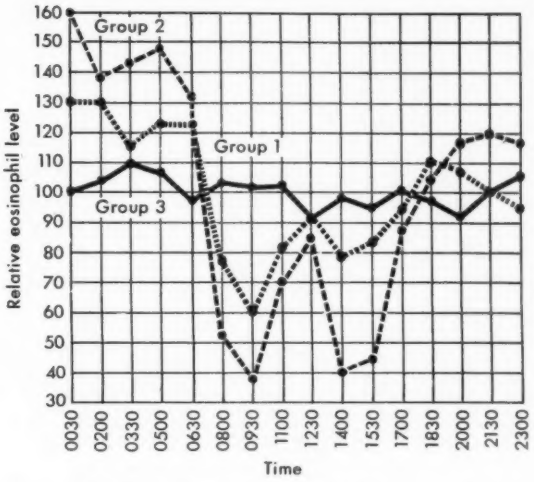

FIGURE 7. Obliteration of eosinophil rhythm in man in verified adrenocortical insufficiency. Group 2, unlimited activity; group 1, limited activity; group 3, limited activity, adrenal insufficiency.

chronous in the second profile as compared with the first. Evidence for a critical role of the adrenal cortex in maintaining this rhythm was not obtained.

From the foregoing illustrative examples it would appear that the factors which determine the phase relations of human 24 hour rhythms may vary from one rhythm to another, as do those physiologic factors which maintain a given rhythm. It seems important, however, that several cellular rhythms are obliterated by adrenalectomy (figure 10).[5, 22-24] A discussion of the present state of our exploration of factors underlying 24 hour rhythms has been presented elsewhere.[25]

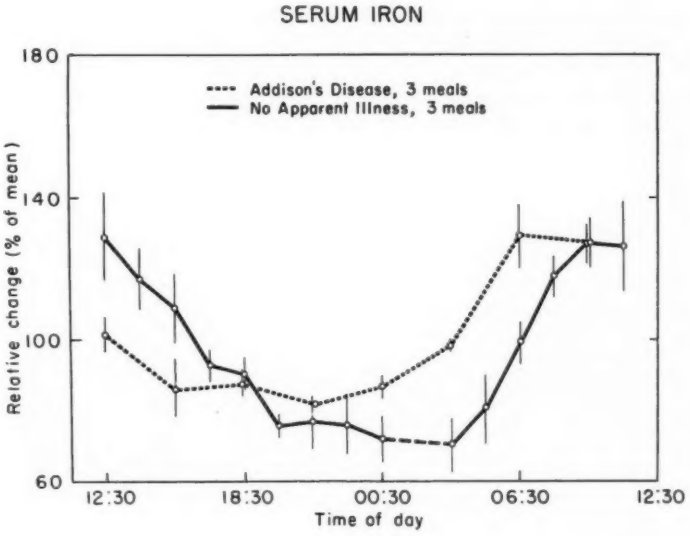

FIGURE 8. Persistence of serum iron rhythm in man in verified adrenocortical insufficiency.

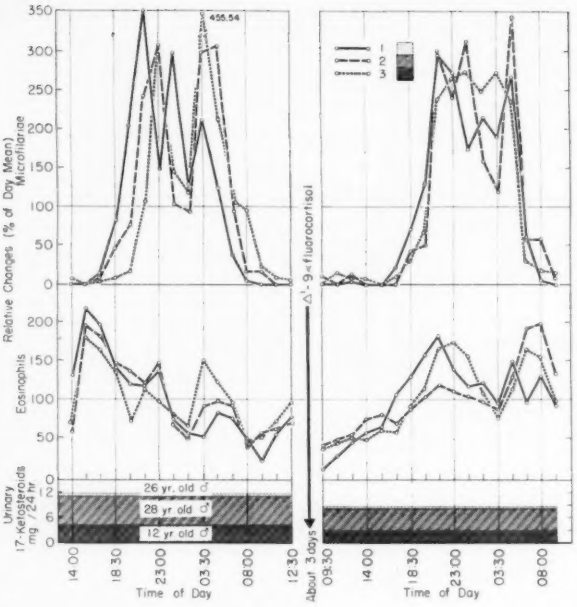

FIGURE 9. Counts of blood eosinophils and *W. bancrofti* microfilariae, before and after Δ^1-9α-fluorocortisol (see text).

Implications and Applications of Periodicity Analysis

Functional integration; synchronization—By appropriate standardization, the timing of rhythms in different parts of the body can be reproducibly described and rhythmic interactions analyzed. Let us describe as "synchronization" a state in which time relations among periodic functions are defined by reproducible phase differences, plus, minus or zero (locked phase relations). More than synchrony is then meant by synchronization, the former term being reserved for events coincident in time and the latter describing defined phase differences as well as synchrony among integrated body functions, i.e., frequency synchronization.

Figure 11 may serve to illustrate several aspects of synchronization at different levels of organization. We are here dealing with data on inbred mice kept under comparable physical environmental conditions, in the absence of stimulation other than daily routine. First we may examine synchronization in a given organ such as the adrenal cortex. We find mitotic rhythms in its parenchyma and stroma as roughly synchronous (with the sampling schedule used, the phase difference appears to be zero). Turning next to synchronization among organs or tissues, we compare the timing of mitotic rhythm in liver parenchyma, adrenal cortex and skin epidermis.[25,26] Rhythms in liver and skin, at the "magnification" (sampling interval) used, are roughly synchronous (the phase difference again is zero). But mitoses in either liver parenchyma or skin epidermis are out of phase with adrenocortical mitoses, in a synchronized state. To the foregoing time relations one may counterpose

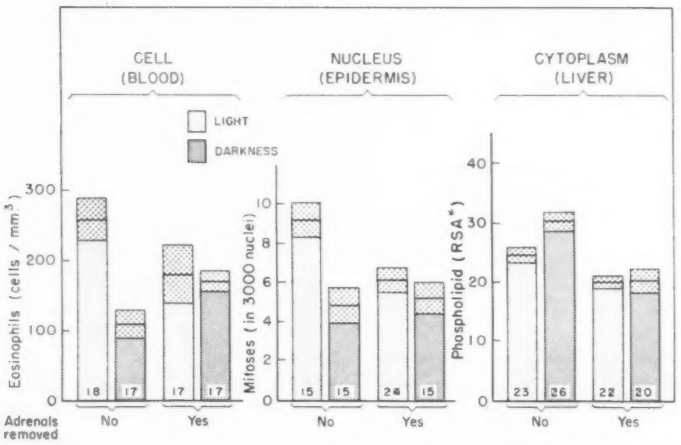

FIGURE 10. Obliteration of rhythms in blood eosinophils, epidermal mitoses and hepatic phospholipid metabolism in the mouse in verified adrenocortical insufficiency.

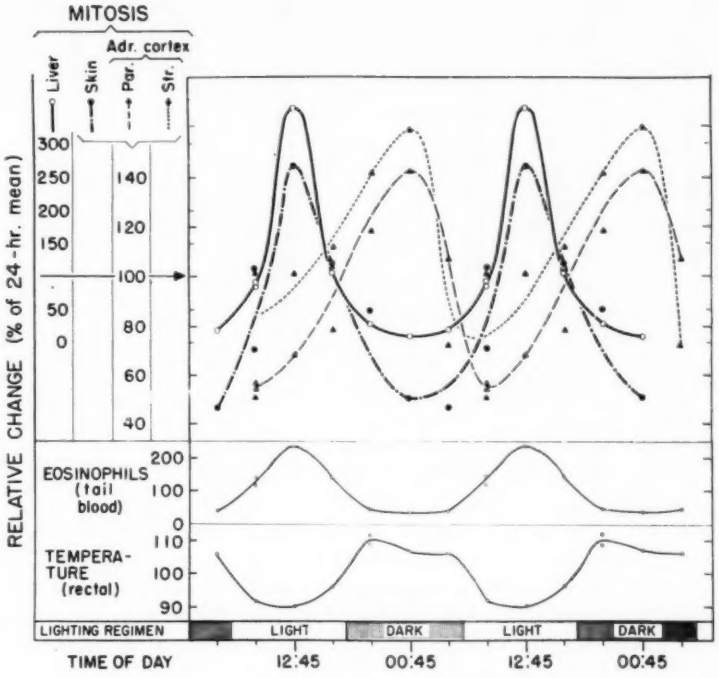

FIGURE 11. Rhythms of mitoses in different tissues, blood eosinophils, rectal temperature, and the lighting regimen. *Partium consensus in tempore*, illustrative of "synchronization" of time relations that are not necessarily causal (see text).

functional synchronization among different levels of organization, the curves for rhythms in mitoses, blood eosinophils and rectal temperature being cases in point (figure 11). Finally, we find synchronization (of functions at any or all levels of organization) with environmental factors, e.g., lighting regimen, in the mouse (figure 11).

Significance of phenomenon—Adaptation—Adaptively useful functions are integrated into smooth neural, endocrine and metabolic interactions, many aspects of which are 24 hour periodic. "Resolution" of such interactions by periodicity analysis in different parts of the body reveals a new facet in time of the mutually coordinated activity of different organs. Phase relations of various periodic events thus yield a map for exploring a *partium consensus in tempore*. The changes of cyclic characteristics such as period, amplitude, phase, shape

TABLE 2

RELATION OF 24 HOUR RHYTHMS IN BODY TEMPERATURE AND EOSINOPHIL COUNT, ON ROUTINES MAINTAINED FOR DIFFERING TIME PERIODS; CORRELATION COEFFICIENTS (r) AND THEIR SIGNIFICANCE (P)

SUBJECT	ROUTINE*	FOR A PERIOD OF	r	P
A	N	Years	−0.63	0.01
B	N	Two days†	−0.04	0.80
C	D and N	Years	−0.69	0.003
D	D and N	Two days†	−0.03	0.80
E	D	Years	−0.56	0.025
F	D	Years	−0.53	0.037

*D, active by day; N, active by night.

†Note lack of correlation during shift in routine.

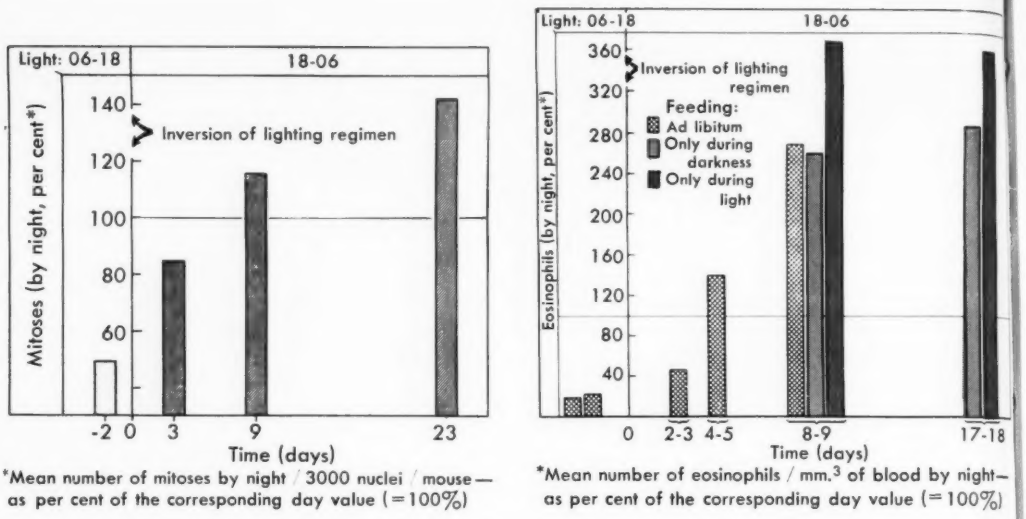

FIGURE 12. Gradual shift of rhythms in pinnal mitoses and blood eosinophils in the mouse following abrupt inversion of lighting regimen. Note difference in "shift time," suggestive of transient "desynchronization" (see text).

and level, as they occur under unusual or adverse conditions, in turn, yield a measure of adaptive potential. What we have earlier summarized as synchronization may be a requisite for optimal body efficiency, even though transient desynchronization, during changes of routine, may not have appreciable ill effects.[27]

Such transient desynchronization of rhythms in blood eosinophils and rectal temperature of human beings is suggested by table 2. Desynchronization of rhythms in blood eosinophils and epidermal mitoses in the mouse is suggested by figure 12, since the inversion of the two rhythms following abrupt reversal of illumination takes different periods of time (unequal shift times). But the fact that basic periodic body functions[28] shift only gradually following abrupt changes in environmental synchronizer is in itself of interest, irrespective of the shift times involved. We witness "resistance" to sudden changes of the environment, until the body has "made certain" the changed schedule is to be maintained! Integrative periodic functions may have an important adaptive value by maintenance of an old schedule until a more basic sequence of periodic metabolic events in the cell also can shift to a "sufficiently" long-continued new schedule.[28, 29]

Endocrinology—The importance of the adrenal cycle has been discussed.[4, 30, 31] Here we may refer, in addition, to hormone-target relations in the light of periodicity analysis. Cycles

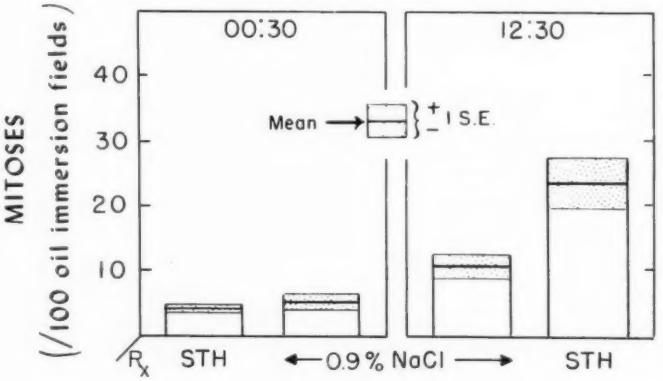

FIGURE 13. Hepatic mitotic activity in mice given a three day course of STH (daily at ~16:30) is significantly higher than in controls given saline, if livers are removed at noon on the day following injection (right-hand section of figure). This effect is not apparent in materials removed at midnight (left-hand section).[32]

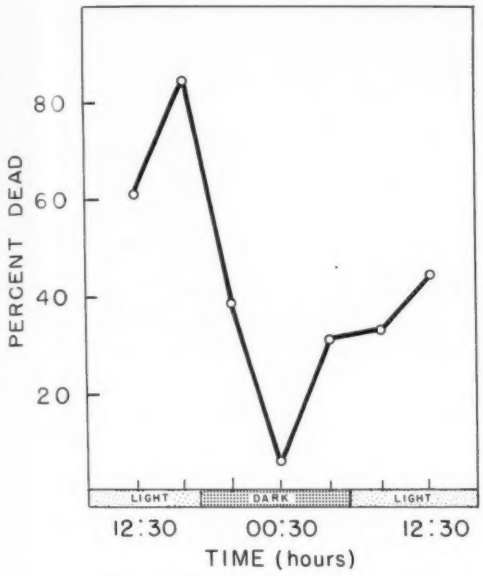

FIGURE 14. Differential lethality of *Esch. coli* endotoxin when given at different times to comparable mice. These admittedly complex 24 hour rhythms (characteristics in time of functional integration and environmental adaptation) can critically determine the ability to withstand damage. (For such *horae variae resistentiae* see also figure 3.)

at the level of the cell can critically determine hormone effects. In figure 13 it is seen that pituitary growth hormone injection is associated with increased mitotic count in intact mouse liver in one phase of cycle but not in another.[32,33]

Experimental pathology—Many students of disease regard 24 hour periodicity merely as a source of variation which one "controls" by "working at the same time of day" (perhaps chosen on the basis of convenience rather than pertinence). Figure 13 illustrates one shortcoming of this approach. Periodic changes of the body also have been discussed without more rigorous evaluation of cyclic characteristics, simply as "stress reactions." If, however, as we suggest, physiologic periodicity is an important (though complex) entity of the experimental pathologist, exposure to the same agent in different phases of 24 hour rhythm may have a drastically different outcome. (One can keep the "stressor" constant and allow the physiologic state to vary.) With regard for genetics, past history and experimental environment[5] one may then test a potentially noxious agent on separate groups of comparable mice, at times of different physiologic states.

With the foregoing in mind, we may turn again to figure 3, presenting results of exposure to noise at the times of eosinophil high and low,[10,11] or we may study effects of *Escherichia coli* endotoxin injection as a function of 24 hour periodicity (figure 14). In each instance periodic physiologic changes account for the difference between life and death, be it from audiogenic convulsion or from endotoxin-induced shock (other things being kept as comparable as feasible). Moreover, the highest susceptibility to convulsions will be associated with one physiologic state,[10,11] and that to endotoxin with another.[34,35] Such physiopathologic interactions (figures 3 and 14) are an important domain of periodicity analysis, done for evaluating the cyclic factors underlying changes in susceptibility to disease.

This periodicity analysis is not easy, since external-internal interactions resulting in 24 hour rhythms involve different numbers and types of intermediate steps, in the case of different rhythms or species or both. Such factors of different complexity, in turn, call for an approach differing from case to case. But these tasks are important to medical research, when we are dealing with changes critically determining our ability to withstand damage (figures 3 and 14). We have approached these physiologic 24 hour changes as entities in their own right. They represent characteristics *in time* of functional integration and, perhaps, of the success or failure of environmental adaptation. The extent to which analyses of these physiologic changes will prove clinically useful will be decided by further work, to be visualized only in a spirit of hope rather than satisfaction.

ACKNOWLEDGMENT

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Effect of Rice Diet on Diabetes Mellitus Associated With Vascular Disease

WALTER KEMPNER, RUTH LOHMANN PESCHEL AND CLOTILDE SCHLAYER*

Duke University School of Medicine, Durham, North Carolina

BECAUSE of a high incidence of advanced vascular disease among our patients with diabetes mellitus, we have for the past 15 years treated numerous diabetic patients with the rice diet. Since more than 90 per cent of the calories in this diet are derived from carbohydrates, it was anticipated that increased amounts of insulin would be necessary to keep the blood sugar at its previous level. However, the opposite proved to be true. As previously reported,[1-5] not only is the rice diet well tolerated but in many instances the blood sugar and the insulin requirements decrease.

This paper deals with the effect of the rice diet on some vascular complications, particularly diabetic retinopathy, as well as with its effect on blood and urine chemical findings, especially blood sugar and insulin levels. Findings are given for 100 consecutive patients who were first examined by us between May 1944 and September 1955 and who followed the rice diet more or less strictly for at least three months. The period of observation in these 100 cases ranged from three months to 11 years and averaged 22 months. Nine patients died during the period reported here.

Clinical and Laboratory Data

Table 1 gives the average figures before and after treatment for blood sugar, urine sugar, insulin dosage, serum cholesterol, weight, blood pressure, heart size, blood nonprotein nitrogen, phenolsulfonphthalein excretion and urine protein, as well as averages for duration of diabetes, period of observation, age and sex, and incidence of vascular calcifications on x-rays.

Blood sugar—In 22 cases the fasting blood sugar remained relatively unchanged. In 78 cases a change of 20 mg. or more per 100 cc. was found. In 15 the blood sugar increased, the average levels being 140 mg. before treatment and 241 mg. after treatment. In the remaining 63 of the 78 cases the blood sugar level decreased, with averages of 236 mg. before treatment and 135 mg. after treatment.

*Department of Medicine, Duke University School of Medicine, Durham, North Carolina.

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This paper was written for Dr. Otto Warburg in honor of his seventy-fifth birthday.

TABLE 1

EFFECT OF RICE DIET ON 100 PATIENTS WITH DIABETES MELLITUS; CLINICAL AND LABORATORY DATA (AVERAGES)

Average age of patients, 51 years (19 to 71)
Sex distribution, 46 men and 54 women
Average known duration of diabetes, nine years (0 to 33)
Average period of observation, 22 months (3 to 137)

	Before diet	*After diet*
Fasting blood sugar (mg. per 100 cc.)	202	155
Insulin (units)	25	17
Urine sugar (gm. in 24 hours)	21.1	4.2
Cholesterol (mg. per 100 cc. of serum)	297	239
Weight (kg.)	71.3	64.0
Blood pressure (mm. Hg)	179/97	151/85
Heart size (heart-chest ratio)	0.48	0.45
Incidence of arteriosclerosis (x-rays) (per cent)	66	
Nonprotein nitrogen (mg. per 100 cc. of blood)	42	37
Phenolsulfonphthalein excretion (per cent in two hours)	55	49
Proteinuria (gm. per 1000 cc. of urine)	0.36	0.19

Insulin—Twenty-eight patients did not take insulin either at the beginning or at the end of treatment. In 21 of the 72 cases in which the patients did take insulin the dosage was not changed; in 51 it was changed. Insulin dosage was increased in nine cases, including four in which the patients started without insulin (averages, 22 units before and 44 units after treatment). It was decreased in 42 cases. The average dosages in these cases were 39 units before treatment and 16 units after treatment; in 18 cases with an average initial insulin requirement of 26 units, insulin could be completely discontinued.

Glycosuria—Sixty-six of the 100 patients did not have glycosuria either at the beginning or at the end of treatment. In three of the 34 cases in which the patients had glycosuria, there was an increase in the amount excreted; in two of these three cases the average increase was from zero to 11.2 gm. in 24 hours, and in the third case the amount increased from 4 to 14.6 gm. in 24 hours. In 31 of the 34 cases in which the patients had glycosuria, there was a decrease in the amount excreted: from 28.1 to 8.1 gm. in 24 hours (averages), nine cases; from 4 plus to 3 plus, three cases; from 4 plus to 1 plus, one case; from 22.1 gm. in 24 hours (average) to zero, eight cases; from 4 plus to zero, four cases; from 2 plus to zero, three cases; and from 1 plus to zero, three cases.

Serum cholesterol—Twenty of the 100 patients had a serum cholesterol concentration of 220 mg. or less per 100 cc. at the beginning of treatment. In 13 of these cases the concentration increased, the averages being 191 mg. before treatment and 232 mg. after treatment. In two cases the cholesterol concentration remained unchanged. In five it decreased (average, 201 mg. to 174 mg.).

Eighty patients had a serum cholesterol concentration of 221 mg. or more per 100 cc. at the beginning of treatment. The concentration increased in 12 of these cases (averages, 303 mg. before treatment and 352 mg. after treatment). In the other 68 cases the cholesterol concentration decreased, the average values being 325 mg. before treatment and 227 mg. after treatment.

Blood pressure—Ten patients had blood pressures of 129/88 or less at the beginning of treatment; the average readings in these 10 cases were 122/77 before treatment and 129/82 after treatment.

Ninety patients had blood pressure readings of 135/82 or more (average, 185/99) at the beginning of treatment. Their average blood pressure after treatment was 153/85. In 19 cases the blood pressure returned to normal (118/75, average).

Heart size—Chest films of 87 patients are available for comparison before and after treatment (no digitalis after beginning of rice diet). In 59 cases the heart-chest ratio was less than 0.50 before treatment; it decreased from 0.44 to 0.43 (averages). In 28 cases the heart-chest ratio was 0.50 or more before treatment. It decreased from 0.56 to 0.50 (averages). In no case did the heart become larger in size.

Electrocardiogram—Electrocardiograms of 86 patients are available for comparison before and after treatment (no digitalis). Fifty of the 86 patients had a normal electrocardiogram at the beginning of treatment. In 46 cases it remained normal, and in four cases

abnormal findings were observed: infarct, one case; T_1 inverted, two cases; and diphasic T_1, one case.

Thirty-six of the 86 patients had an abnormal electrocardiogram at the beginning of treatment; four had previous infarction, five had bundle-branch block, and 27 abnormal T_1. In 15 of these cases the abnormal findings persisted (four previous infarction, five bundle-branch block, six inverted or diphasic T_1). In five cases the electrocardiographic findings became worse; in three the diphasic T_1 became inverted, and in two with inverted T_1 a bundle-branch block and an infarction developed, respectively. In 16 cases the electrocardiogram improved; the T_1, which had been inverted in six, diphasic in five, and flat in five, became upright.

Nonprotein nitrogen—Sixty of the 100 patients had a nonprotein nitrogen level of 40 mg. or less per 100 cc. of blood at the beginning of treatment. In 20 of these cases the nonprotein nitrogen increased, the averages being 31.1 mg. before treatment and 39.6 mg. after treatment. In three cases the level remained unchanged. In 37 there was a decrease in the nonprotein nitrogen, from 35.2 mg. before to 30 mg. after treatment (averages).

Forty patients had a nonprotein nitrogen level of more than 40 mg. per 100 cc. of blood at the beginning of treatment. In six of these cases the level increased from an average of 52 mg. before treatment to an average of 64 mg. after treatment. In two the level remained unchanged, and in 32 there was a decrease, from an average of 83 mg. before treatment to an average of 38 mg. after treatment.

Phenolsulfonphthalein excretion—Data on phenolsulfonphthalein excretion before and after treatment are available for 77 of the 100 patients. In only 11 cases was the initial phenolsulfonphthalein excretion 75 per cent or more in two hours. Including these, in 59 cases there was an initial phenolsulfonphthalein excretion of 40 per cent or more in two hours. In 39 of these 59 cases the percentage of phenolsulfonphthalein excreted decreased from an average of 64.7 before treatment to 50.7 after treatment. In two cases the excretion remained unchanged. In 18 it increased, the averages being 60.9 per cent before treatment and 70.1 per cent after treatment.

Eighteen patients had an initial phenolsulfonphthalein excretion of less than 40 per cent in two hours (range, zero to 39 per cent). Of these, nine showed a decrease, from an average of 33 per cent before to an average of 25 per cent after treatment. In one case the excretion remained unchanged. In eight cases it increased, the average before treatment being 20 per cent and the average after treatment 35 per cent.

Proteinuria—Thirty-three patients did not have proteinuria either at the beginning or at the end of treatment. In 10 of the 67 cases with proteinuria, the amount increased from an average of 0.20 gm. per 1000 cc. before treatment to an average of 0.40 gm. per 1000 cc. after treatment. In four cases the amount of protein in the urine did not change, and in 53 it decreased (in 32 from an average of 0.88 gm. before to an average of 0.41 gm. after treatment; in 21 from an average initial level of 0.24 gm. to zero).

Retinopathy—Tables 2 and 3 show the incidence and course of retinopathy, the frequency of renal disease, and duration of diabetes. Of the 100 patients, 68 had advanced retinal involvement.

In 48 cases (44 with comparable photographs) there was specific diabetic retinopathy manifested by capillary aneurysms, punctate, preretinal or vitreous hemorrhages, waxy exudates, neovascularization and retinitis proliferans, with or without other changes in the retina (renal, hypertensive, arteriosclerotic). Thirty of the 48 patients had the most severe form of diabetic retinopathy, retinitis proliferans. Diabetic retinopathy was considered improved if the eyeground photographs after treatment showed marked regression of "diabetic" hemorrhages, exudates, aneurysms or retinitis proliferans.

In 13 of the 44 cases in which photographs are available for comparison, these showed marked improvement. In one case "diabetic" hemorrhages and aneurysms disappeared completely and have not recurred during three years of observation. In eight cases these changes disappeared to a large extent. In four

TABLE 2

INCIDENCE OF RETINOPATHY IN 100 DIABETIC PATIENTS TREATED WITH RICE DIET, AND ITS RELATION TO RENAL DISEASE

	NUMBER OF PATIENTS	AGE* (Years)	KNOWN DURATION OF DIABETES* (Years)	PERIOD OF OBSERVATION* (Months)
Specific diabetic retinopathy	48	48	14	19
(Without renal disease)	(19)	(53)	(15)	(19)
(With renal disease)	(29)	(44)	(14)	(19)
Nonspecific vascular retinopathy	20	53	5	33
(Without renal disease)	(13)	(53)	(5)	(41)
(With renal disease)	(7)	(54)	(5)	(18)
No retinopathy	32	55	4	19
(Without renal disease)	(29)	(54)	(3)	(19)
(With renal disease)	(3)	(61)	(11)	(23)

*Averages.

cases, in addition to improvement of hemorrhages, there was a considerable clearing of retinitis proliferans; the patients in these four cases have been observed for periods of four months, 10 months, five years and five years, respectively.

Twenty patients (19 with comparable photographs) did not have specific diabetic retinopathy as defined in the foregoing discussion but had other forms of retinopathy (renal, hypertensive, arteriosclerotic) manifested by vascular thromboses, hemorrhages, exudates, and papilledema. This retinopathy was considered improved if the eyeground photographs after treatment showed either complete disappearance or considerable clearing of the hemorrhages or exudates or complete disappearance of the papilledema. Eleven of the 19 patients of whom comparable photographs are available showed marked improvement.

In only one of the 32 cases in this series in which the patients did not have retinopathy at the beginning of treatment did it develop during the period of observation (exudates).

TABLE 3

EFFECT OF RICE DIET ON RETINOPATHY IN 63 PATIENTS WITH DIABETES

	NUMBER OF PATIENTS	PERIOD OF OBSERVATION (Months) (Average and Range)
*Specific diabetic retinopathy**		
Eyeground photographs available for comparison	44	19 (4-102)
Progression of lesions	9	28 (4-102)
Lesion improved in one eye, progressed in other	7	19 (4-76)
No change	15	8 (4-48)
Improved	13	25 (4-60)
*Nonspecific vascular retinopathy**		
Eyeground photographs available for comparison	19	33 (4-137)
Progression of lesions	3	8 (5-13)
No change	5	10 (4-21)
Improved	11	52 (8-137)

*Comparable photographs are not available of four patients with specific diabetic retinopathy and one with nonspecific vascular retinopathy.

Representative Case Histories

Figures 1 through 6 are eyeground photographs taken before treatment and after 3½ to 60 months of treatment with the rice diet.

Case 1—The patient in figure 1, a 54 year old woman, was first seen in March 1949. She had had known diabetes mellitus for 10 years. For the first few years there was good control of the disease by diet, and she did not take insulin. Since 1947 she had taken 25 units of insulin daily. Three months before we saw her, she noted the beginning of impairment of vision. One month before we saw her, she suddenly was unable to read headlines with her left eye. At the time we examined her, her vision was somewhat improved, and she could

pick out a few words of smaller headlines with her left eye. Blood pressure had increased for the past 10 years.

The rice diet was started in March 1949.

Laboratory data—Findings at the first examination in March 1949 and in September 1952 were as follows:

	1949	*1952*
Blood pressure (average)	234/108	180/90
Insulin (units)	25	18
Blood sugar, fasting (mg. per 100 cc.)	189	166
Urine sugar	0	0
Cholesterol (mg. per 100 cc. of serum)	225	224
Phenolsulfonphthalein excretion (per cent in two hours)	52	
Albuminuria (gm. per 1000 cc.)	0	0.16
Nonprotein nitrogen (mg. per 100 cc. of blood)	44	50

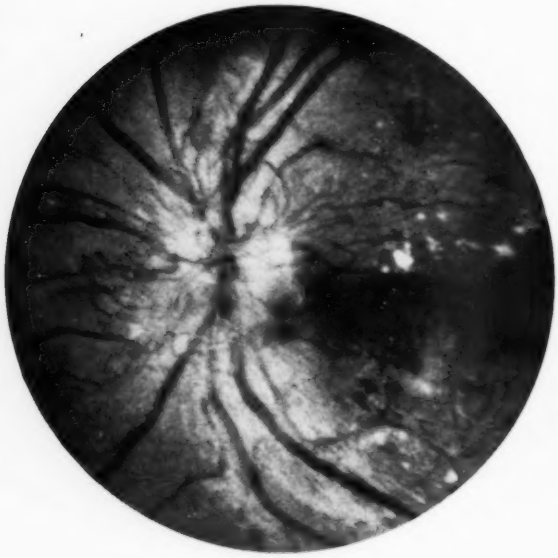
Vision—In 1949 the patient could see well with the right eye, and with the left she could read small headlines with difficulty. There were hemorrhages (large and pinpoint), aneurysms and numerous cottony and hard exudates throughout both fundi, the left macula being more involved than the right. In 1952 vision was normal. Both fundi showed a few sprinkles of exudates, without hemorrhages or aneurysms.

Case 2—The patient represented in figure 2 was a 24 year old man first seen in August 1950. He had a nine year history of diabetes mellitus. There was good control with diet and insulin; he had not had coma, but acidosis had occurred at the ages of 14, 17 and 21 years. He was asymptomatic until January 1949, when the glare of the sun caused difficulty in vision. There were carbuncles on both arms at the sites of insulin injections. Insulin dosage had increased to 85 units. Hemorrhages were found in the eyes. In February 1950 he experienced difficulty in reading because the lines blurred. When driving, the lights were out of focus. His vision was dim,

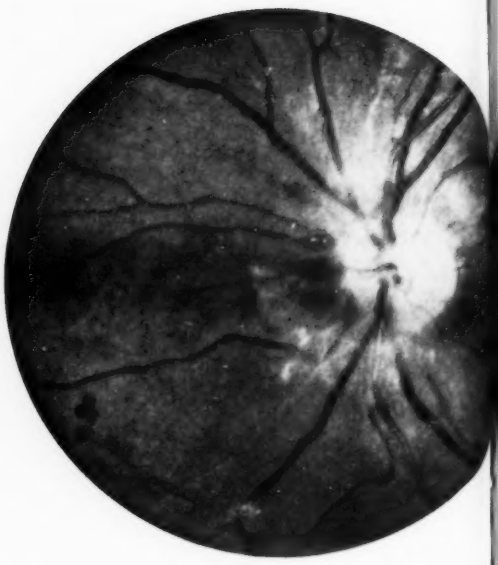
3-14-49

9-25-52

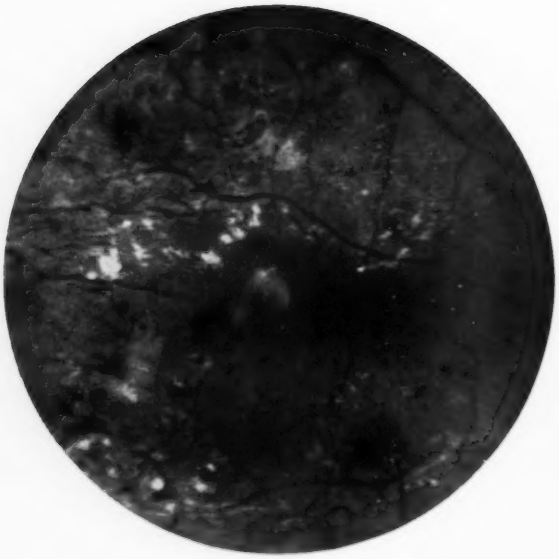
FIGURE 1. Case 1.



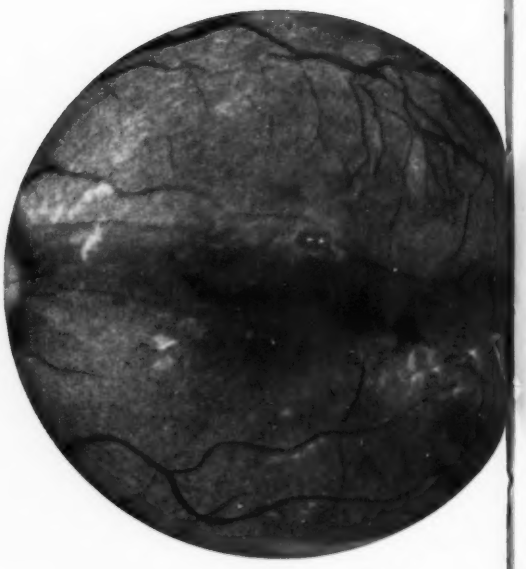
8-18-50



8-16-55

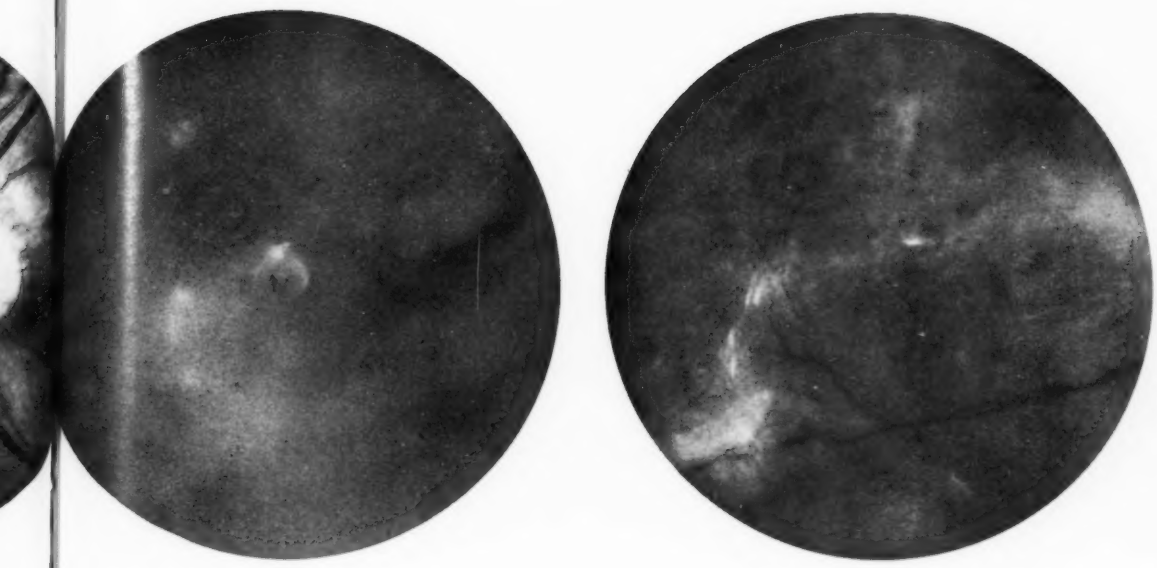


8-18-50



8-16-55

FIGURE 2. Case 2.



10-20-50 10-12-55

FIGURE 3. Case 3.

and he could not read the signs on buses.

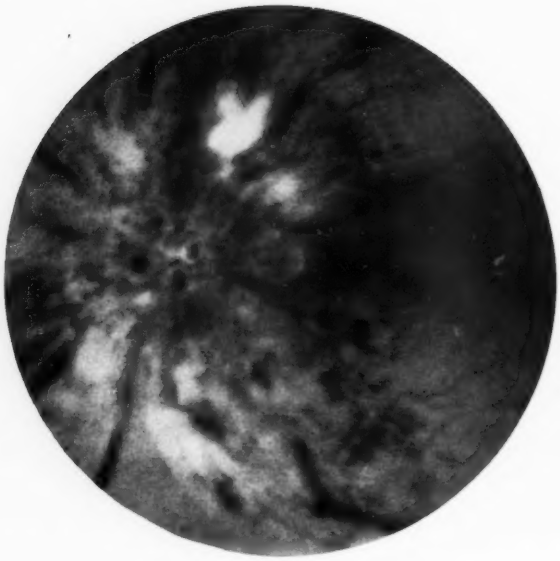
The rice diet was started in August 1950.

Laboratory data—Findings at the first examination in August 1950 and in August 1955 were as follows.

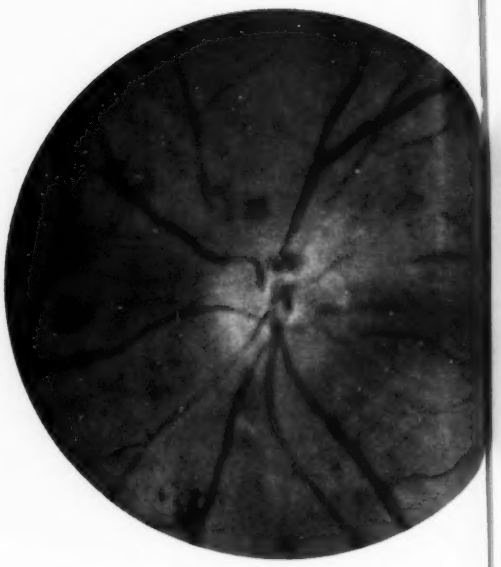
	1950	*1955*
Blood pressure (average)	126/80	135/90
Insulin (units)	75	42
Blood sugar, fasting (mg. per 100 cc.)	91	272
Urine sugar (gm. in 24 hours)	0	1 plus
Cholesterol (mg. per 100 cc. of serum)	165	156
Phenolsulfonphthalein excretion (per cent in two hours)	73	65
Albuminuria (gm. per 1000 cc.)	0.32	0.28
Nonprotein nitrogen (mg. per 100 cc. of blood)	33	43

Vision—In 1950 the patient could read ⅜ in. print. The disks were obscured by marked neovascularization and beginning retinitis proliferans. There were numerous round and flame-shaped hemorrhages, capillary aneurysms, and hard and cottony exudates bilaterally. In 1955 the patient could read small print with his left eye and ½ in. print with the right eye. The right disk was obscured by a hazy veil, but the largest part of the retina, especially the macular region, was almost clear. There were no hemorrhages or exudates. The disk on the left was well outlined. Neovascularization had disappeared, and hemorrhages, exudates and aneurysms had almost completely disappeared.

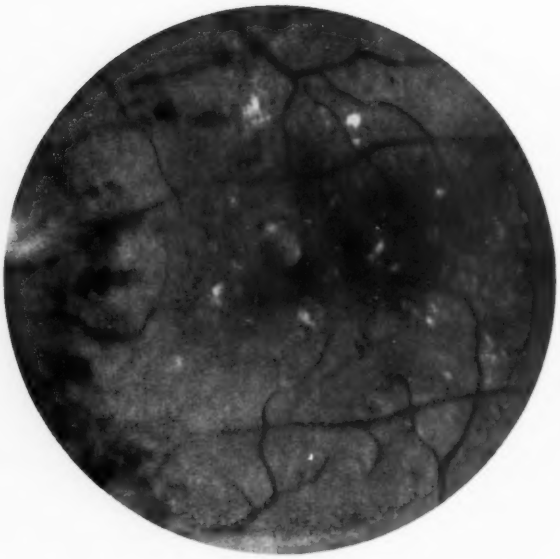
Case 3—A 60 year old woman was first seen in October 1950 (figure 3). Her past history included diabetes mellitus for two years, and weight loss for 16 years although she ate well. In 1948 urinalysis showed 2 plus sugar. A diabetic diet was prescribed but she did not take insulin. One and a half years before we saw her she had visual difficulty. Hemorrhages were found in the right eye. Treatment consisted of RUTORBIN® and 10 units of insulin.



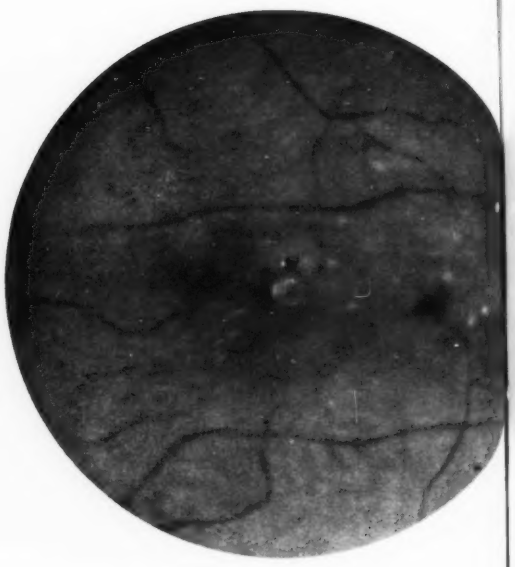
4-12-51



7-25-51



4-12-51



7-25-51

FIGURE 4. Case 4.

Visual impairment in the right eye persisted. Five weeks before we saw the patient she had sudden impairment of vision in the left eye.

The rice diet was started in October 1950.

Laboratory data—The findings in October 1950 compared with those in October 1955 were as follows.

	1950	*1955*
Blood pressure (average)	186/90	170/80
Insulin (units)	14	0
Blood sugar, fasting (mg. per 100 cc.)	161	95
Urine sugar	0	0
Cholesterol (mg. per 100 cc. of serum)	335	228
Phenolsulfonphthalein excretion (per cent in two hours)	64	40
Albuminuria (gm. per 1000 cc.)	0	0.16
Nonprotein nitrogen (mg. per 100 cc. of blood)	39	37

Vision—In 1950 the patient could see contours of large objects with the right eye. With the left eye there was light perception only. There were fundal hemorrhages bilaterally, especially extensive in the left macular region. Marked proliferative changes were noted in both fundi. In 1955 the vision in the right eye had improved. The patient could make out faces and read signs and large newspaper print. With the left eye there was light perception only. There were no fundal hemorrhages or exudates in the right eye; except for proliferative changes around the disk, the retina, especially the macular region, was considerably clearer. Examination of the left eye showed extensive retinitis proliferans, with no hemorrhages.

Case 4—The patient whose eyeground photographs are shown in figure 4 was a 42 year old man first seen in April 1951. Diabetes mellitus had been diagnosed three and a half years previously. He had lost 30 lb., and the blood sugar level at that time was 157 mg. per 100 cc. Treatment consisted of restriction of sweets, and 15 units of insulin. Blood pressure was elevated. Two months before we saw the patient he had blurred vision in his right eye. Blood pressure was 230 systolic, albuminuria was noted, and a hemorrhage was found in the right eye. He was given a salt-poor diet. The vision in the right eye cleared; however, that in the left became cloudy.

The rice diet was started in April 1951.

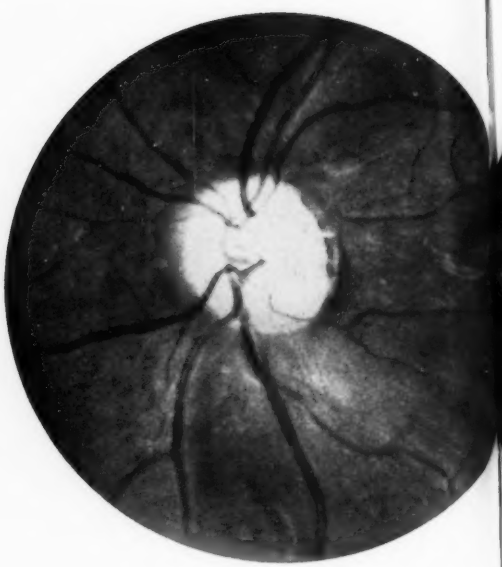
Laboratory data—Comparative findings in April 1951 and in July 1951 were as follows.

	April	*July*
Blood pressure (average)	220/120	143/80
Insulin (units)	15	0
Blood sugar, fasting (mg. per 100 cc.)	85	142
Urine sugar	0	0
Cholesterol (mg. per 100 cc. of serum)	289	183
Phenolsulfonphthalein excretion (per cent in two hours)	26	
Albuminuria (gm. per 1000 cc.)	2.8	0.22
Nonprotein nitrogen (mg. per 100 cc. of blood)	81	70

Vision—In April the patient could see well with the right eye, but had blurred vision with the left. Bilateral papilledema was noted, and numerous hemorrhages and exudates in both eyes. There were capillary aneurysms. In July the patient's vision was normal. The left disk was clearly outlined. The right disk was still slightly hazy but greatly improved. There were a few hemorrhages and small hard exudates, and fewer aneurysms.

Case 5—A 29 year old man (figure 5) first seen in May 1952 had had known diabetes mellitus for 19 years. The diabetes was under good control with 60 to 80 units of insulin daily, and later the dosage was 48 units. There was no history of coma or acidosis, and the urine was almost always sugar-free. For five years before we saw him the patient had albuminuria and hypertension. Blood pressure at a recent examination prior to May 1952 was 180/110. In November 1951 he had an episode of blurring of vision and spots before the eyes. Small hemorrhages were found, and

5-14-52



11-2-55

FIGURE 5. Case 5.

subsequently he had repeated episodes of blurred vision.

The rice diet was started in May 1952.

Laboratory data—Examinations in May 1952 and in November 1955 gave the following findings.

	1952	*1955*
Blood pressure (average)	214/130	141/89
Insulin (units)	62	42
Blood sugar, fasting (mg. per 100 cc.)	58	78
Before lunch	225	177
Before dinner	78	61
Urine sugar (gm. in 24 hours)	8	0
Cholesterol (mg. per 100 cc. of serum)	346	209
Phenolsulfonphthalein excretion (per cent in two hours)	34	25
Albuminuria (gm. per 1000 cc.)	1.3	0.62
Nonprotein nitrogen (mg. per 100 cc. of blood)	38	45

Vision—In May 1952 vision was blurred. There were numerous hemorrhages and cottony exudates scattered throughout both fundi. Capillary aneurysms were noted. In November 1952 there was improvement of vision and regression of hemorrhages and exudates. In March 1953, examination showed complete disappearance of hemorrhages, exudates and aneurysms. Between March 1953 and November 1955, the patient had seven checkups, each including eyeground photographs. There was no recurrence of diabetic or other retinopathy. In November 1955 visual acuity was normal; disks were well outlined, and there were no hemorrhages, exudates or aneurysms.

Case 6—The patient represented in figure 6 was a 65 year old woman first seen in August 1955 with a 15 year history of diabetes mellitus. When the disease was diagnosed, the blood sugar was 200 mg. per 100 cc., and the blood pressure was elevated. A general diet was prescribed, restricting carbohydrates, and 40 units of insulin was given daily. The diabetes was fairly well controlled. Over a period of 10 to 15 years before we saw her, the patient had failing vision in the left eye, and had

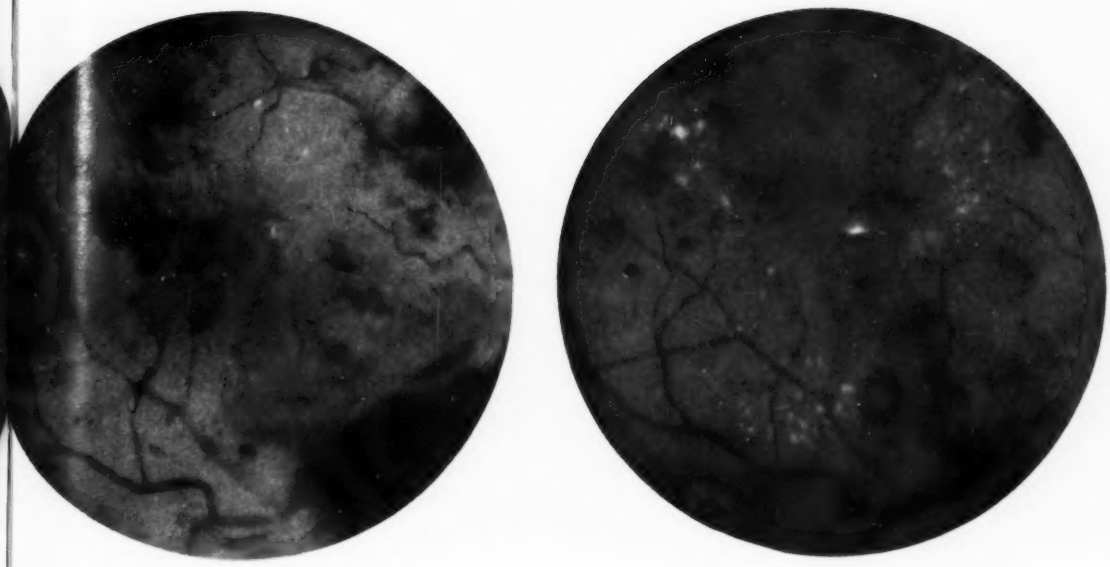


FIGURE 6. Case 6.

noticed failing vision in the right eye for one and a half years. The patient was said to have "bleedings and scars" in the eyes. Rapid impairment of vision occurred in the two month period before we saw her. She could still see objects and read big headlines.

The rice diet was started in August 1955.

Laboratory data—Findings in August 1955 and in December 1955 were as follows.

	Aug.	*Dec.*
Blood pressure (average)	190/100	146/74
Insulin (units)	40	20
Blood sugar, fasting (mg. per 100 cc.)	161	136
Urine sugar	0	0
Cholesterol (mg. per 100 cc. serum)	226	191
Phenolsulfonphthalein excretion (per cent in two hours)	68	
Albuminuria (gm. per 1000 cc.)	0.1	0
Nonprotein nitrogen (mg. per 100 cc. of blood)	40	30

Vision—In August 1955 the patient could read large print with either eye. The disks were well outlined, and there were numerous hemorrhages and hard exudates in both fundi. In the right eye there was inferior temporal vein thrombosis with massive hemorrhage. Capillary aneurysms were noted. In December 1955 the patient could read newspaper print. Disks were well outlined, and marked regression of hemorrhages and exudates was noted. Capillary aneurysms were still present.

Discussion

It has been known since 1943[1-5] that patients with diabetes mellitus not only tolerate the rice diet well but also are often benefited by it. (The rice diet contains 565 to 570 gm. carbohydrate, 20 to 25 gm. protein, less than 5 gm. fat, and 70 to 120 mg. sodium per 2400 calories.) The present survey of 100 patients shows again that the average blood sugar levels and average insulin requirements decrease. Although this group included many patients with severe diabetes, ketosis occurred only once. Acidosis did not occur; on the contrary, the plasma carbon dioxide-combining power

increased in the majority of cases and moved away from the acid toward the alkaline side.

Patients who were obese were urged to reduce. However, changes in blood sugar levels, insulin requirements, cholesterol levels, blood pressure, and so on occurred both in patients who lost weight and in those who did not have a significant weight change.

In view of the frequency of the development of arteriosclerosis in diabetic patients, the decrease in the serum cholesterol level may be of importance.

The reduction in blood pressure and heart size and the improvement in abnormal electrocardiographic patterns in diabetic patients treated by the rice diet are the same as those found in nondiabetic patients with cardiovascular disease who are treated with the rice diet. This is also true for the decrease in azotemia in cases in which there is renal involvement. An increase in the average phenolsulfonphthalein excretion was not found, and we cannot yet state whether this is because a much longer treatment period may be necessary for this change to occur.[6]

Of particular interest was the effect of the rice diet on diabetic retinopathy. The ophthalmoscopic picture of "specific" diabetic retinopathy differs from that of renal, arteriosclerotic or hypertensive vascular retinopathy. All forms of vascular retinopathy may occur together with the "specific" diabetic retinopathy, as was also found in this series.

Table 2 shows again that diabetic retinopathy develops more commonly in patients who have had diabetes for a long time. In the 52 cases without evidence of diabetic retinopathy the known duration of diabetes prior to the first examination at our institution averaged 4.4 years; the known duration of diabetes in the 48 patients with "specific" diabetic retinopathy averaged 14 years. The table confirms further the frequent coincidence of renal disease and diabetic retinopathy (60 per cent). Table 3 indicates that at least during the period of observation covered by this study the renal, arteriosclerotic and hypertensive changes improved in a significantly higher percentage of cases than did the "specific" retinal changes; the percentages were 55 and 27 per cent, respectively. Hemorrhages, exudates and papilledema heal as well in diabetic patients as they do in nondiabetic patients treated with the rice diet.

Diabetic retinopathy has been considered a sign of irreversible destruction. "The retinal complications of long-standing diabetes are grave and have an unfavorable prognostic significance. Any observation, therefore, is valuable which indicates a favorable influence in at least some patients."[7]

In our group of 48 patients with diabetic retinopathy the incidence of retinitis proliferans, the severest form of diabetic retinopathy, was very high, 63 per cent. Thirteen patients with diabetic retinopathy, four of them with retinitis proliferans, showed marked improvement. In the 26 of the 30 cases of retinitis proliferans in which this lesion did not improve the patients were observed for 3 to 102 months (average, 17 months), compared with observation periods of 4 to 60 months (average, 34 months) in the four cases in which the lesion did improve.

The effect of the rice diet on diabetes mellitus with or without retinopathy has been explained as "due to a reversible inactivation of the pituitary and/or adrenal gland achieving in a conservative and unbloody way what has been tried by hypophysectomy and adrenalectomy."[8] In this connection the report[9] of a case of improvement in diabetic retinopathy after pituitary necrosis might be interesting. This is one of the few instances reported in the literature in which severe diabetic retinopathy disappeared.

The observations of Handler and Georgiade[10] of our department of biochemistry are also interesting along these lines. They studied the effect of proteins on blood sugar in two groups of rats, the first of which received a low protein diet and the second a high protein diet. They found that the rats receiving a low protein diet were much more sensitive to insulin than were the rats receiving a high protein diet, and also that their fasting blood sugar concentrations were lower. This difference in the blood sugar concentrations disappeared when the animals who were on a low protein diet were treated with ACTH. The in-

vestigators concluded from these results that prolonged low protein diet causes the pituitary to secrete less ACTH.

No matter which single factor may cause the effects of the rice diet on diabetes mellitus and its vascular complications, the rice diet contains less sodium, protein and fat than any other diet for treating diabetes mellitus.

Summary

A report is given on 100 consecutive patients with diabetes mellitus associated with vascular disease who were treated with the rice diet. They were followed for from three months to 11 years, and the average period of observation was 22 months. Nine patients died.

The rice diet, which is a high carbohydrate, low protein, low fat, low sodium diet containing 565 to 570 gm. carbohydrate, 20 to 25 gm. protein, less than 5 gm. fat, and 70 to 120 mg. sodium per 2400 calories, was well tolerated. Average insulin requirements as well as average blood sugar levels decreased.

Manifestations of cardiovascular and renal disease such as hypertension, enlargement of the heart, electrocardiographic abnormalities, azotemia and proteinuria improved significantly in the majority of cases. Hypercholesteremia, present in 80 of the 100 cases, decreased in 85 per cent from an average level of 325 mg. to an average level of 227 mg. per 100 cc.

The effect of the rice diet on "specific" diabetic retinopathy (aneurysms; punctate, preretinal, vitreous hemorrhages; waxy exudates; retinitis proliferans) in 44 patients was as follows: progression of lesions, nine cases; improvement in one eye but progression of lesion in other eye, seven; no change, 15; improved, 13. In 19 cases in which the patients had hypertensive, arteriosclerotic or renal retinopathy (papilledema, hemorrhages, exudates, venous thrombosis), the lesions progressed in three, did not change in five, and improved in 11 cases.

Our experience leads us to conclude that an attitude of resignation with regard to the prognosis in diabetes mellitus with vascular complications including diabetic retinopathy is no longer necessary. The course of the disease can be favorably changed by intensive treatment with the rice diet.

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The Selective Placement of Cardiacs in Industry

AN ANALYSIS OF EXPERIENCE AT A LARGE REFINERY

NEILL K. WEAVER*

Tulane University School of Medicine, New Orleans

NEILL K. WEAVER

FOR many years certain workers at the Esso Baton Rouge Refinery who had partially disabling cardiac conditions have been permitted to continue gainful employment. During the past five years, a formal program for the placement of handicapped employees has been in operation. This program utilizes the matching of the worker's capacities with the physical demands of the job to achieve proper placement.[1,2] An understanding refinery management—which fully recognizes the importance of the worker, "the company's most valuable asset"—has contributed greatly to the success of this program.[3]

*Medical Director, Baton Rouge Refinery of the Esso Standard Oil Company; Assistant Professor of Clinical Medicine, and Assistant Professor, Department of Preventive Medicine and Public Health (Occupational Medicine), Tulane University School of Medicine, New Orleans, Louisiana.

Company policies of self-insurance and liberal employee benefits have tended to lessen those legal and economic factors which may act as significant deterrents to the rehabilitation of workers with cardiac disease. In addition, the placement program has enjoyed a high level of cooperation on the part of the plant employees and their union officials. The practicing physicians in the community have come to accept the refinery medical department as a classification center for cardiovascular diseases, and refer their employee patients to it for evaluation of their ability to work. In this setting, the refinery physicians have been able to follow a practice of encouraging rehabilitation at work whenever such a course appeared to be in the best interest of the patient's total health and well-being. It is believed that this approach to the rehabilitation of patients with cardiac disease is in accord with the views expressed by Master and Dack,[4] Kresky and Goldwater,[5] Franco,[6,7] Hellerstein and Goldston,[8] Dennison,[9] and other authors.

Identification of Workers With Heart Disease

Workers with heart disease are identified by various methods. The physician in industry is particularly alert to the early detection of cardiovascular disease through the periodic examination program. The average refinery employee has had four such health inventories during the past five years, and workers with suspected or known disease may be examined much more frequently. Patients report their symptoms or illnesses to the medical department at any time. Workers observed in apparent distress on the job are sent to the medical department immediately by their supervisor, and patients presumed to have heart disease are referred for study and placement by their personal physicians, as mentioned previously.

Evaluation and Placement of Workers With Heart Disease

Once the presence of heart disease is recognized, the affected worker is evaluated by appropriate procedures. These include a carefully taken history, a very thorough physical examination, an electrocardiogram and ballistocardiogram, roentgenographic or roentgenoscopic examinations, laboratory tests, and a study of pulmonary function (ventilation test). The first objective of this evaluation is to arrive at an accurate etiologic and anatomic diagnosis. A second and more important objective is to make a valid appraisal of the patient's functional capacity. Repeated interviews and examinations are of the utmost importance. This is particularly true in cases in which the presence of heart disease is suspected but has not been proved.

The patient's functional ability is determined in relation to those ordinary physical capacities which make up our activities on and off the job—standing, walking, climbing, lifting, carrying, etc. A Physical Capacities Analysis (PCA) form has been devised. On this form, the physician indicates the number of hours permitted for each of the activities during the work day. He is then able, by using practical, meaningful terms, to advise the patient, his family and supervisor regarding the activities permitted.

The various job assignments in the refinery have been subjected to an engineering analysis, based on the same capacities. This is known as the Physical Demands Analysis. A medical-management team, knowing the patient's qualifications and capacities, considers demands or requirements of various jobs. Proper placement of the limited employee is carried out by matching his capacities with the demands of the job (figure 1).

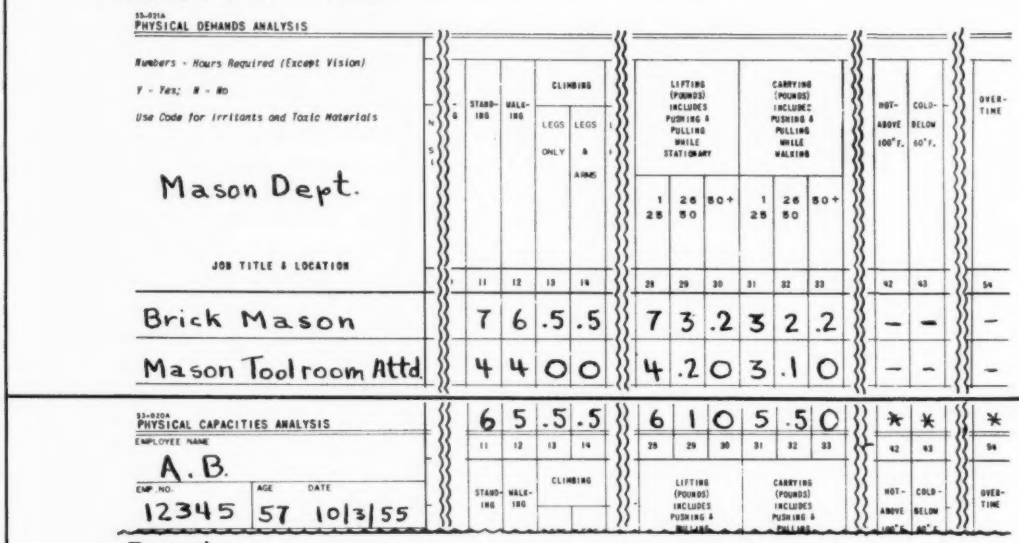
Certain general aspects of the placement procedure are worthy of comment. The welfare of the patient should always receive first consideration. The job should always be a legitimate one, not a makeshift or token assignment in which the worker will be "carried" by fellow employees. The worker should be qualified, or able to qualify, for the job in terms of knowledge, training and experience. The final decision or announcement should be made by a supervisor. We have found this point particularly important in obtaining acceptance by all parties concerned—the patient, his immediate supervisor, his fellow workers and his union representative. This is not so if the decision is made by the patient himself, his own doctor or the industrial physician. It is usually desirable for the older worker to return to the same job, or to a type of work similar to that done before the onset of disability. In addition to this, a careful system for follow-up study, both on the job and in the medical department, is essential to insure suitability of the assignment.

Results of Program for Selective Placement of Employees With Heart Disease

To evaluate the results of the cardiac rehabilitation program, an analysis was made of all employees on the active rolls of the refinery during 1956 whom the company physicians considered limited by heart disease. It should be emphasized that this study was not concerned with employees in whom there exists merely some medical evidence of cardiac abnormality. All employees included for analysis had symptoms or physical findings

MATCHING PHYSICAL CAPACITIES WITH JOB DEMANDS

Clinical Background of Case: Mr. A. B. , age 57 WM Brick Mason. Myocardial infarction June 15, 1955.
Uncomplicated recovery. Angina on walking 3-4 blocks at brisk pace. No evidence of congestive failure. Resumed work October 3, 1955 as Mason Toolroom Attendant. Is asymptomatic at work.



PHYSICAL DEMANDS ANALYSIS

Numbers - Hours Required (Except Vision)
Y - Yes; N - No
Use Code for Irritants and Toxic Materials

Mason Dept.

JOB TITLE & LOCATION

	STAND-ING	WALK-ING	CLIMBING: LEGS ONLY	CLIMBING: LEGS & ARMS	LIFTING (POUNDS) INCLUDES PUSHING & PULLING WHILE STATIONARY: 1-25	26-50	50+	CARRYING (POUNDS) INCLUDES PUSHING & PULLING WHILE WALKING: 1-25	26-50	50+	HOT-ABOVE 100°F.	COLD-BELOW 60°F.	OVER-TIME
	11	12	13	14	28	29	30	31	32	33	42	43	54
Brick Mason	7	6	.5	.5	7	3	.2	3	2	.2	–	–	–
Mason Toolroom Attd	4	4	0	0	4	.2	0	3	.1	0	–	–	–

PHYSICAL CAPACITIES ANALYSIS

EMPLOYEE NAME: A. B.
EMP. NO.: 12345 | AGE: 57 | DATE: 10/3/55

	STAND-ING	WALK-ING	CLIMBING	LIFTING (POUNDS) INCLUDES PUSHING &	CARRYING (POUNDS) INCLUDES PUSHING &	HOT-ABOVE	COLD-BELOW	OVER-TIME
	11 12		13 14	28 29 30	31 32 33	42	43	54
	6 5		.5 .5	6 1 0	5 .5 0	*	*	*

87-230

Remarks

#12. Ability to run is limited; may require rest periods.
#13, 14. Rest may be required after each flight of stairs.
#28, 29, 31, 32. May require rest periods to interrupt periods of effort.
#42 Work must be done at a slower pace at temperature above 92°F.
#43. Work must be done at a slower pace at temperature below 40°F.
#54. Overtime should be minimized.

FIGURE 1

which warranted restriction of physical activities. In the nomenclature of the Criteria Committee of the New York Heart Association, they are classified in Functional Capacity Class II or III, and in Therapeutic Class B (a few patients), C or D (the majority of patients).

The study revealed that 200 (2.8 per cent) of the refinery's 7,140 employees had partially disabling heart disease. During 1956, 19 additional employees were added to the refinery's pool of disabled cardiacs; 13 left the group, one by regular retirement, three by early voluntary retirement, seven by retirement because of disability, and two because of death.

Table 1 shows the causes of the heart disease in the 200 cases. Calcific aortic stenosis was present in two of the five cases in which the heart disease is listed as being due to miscellaneous causes. Two patients in this group had arrhythmias. Paroxysmal supraventricular tachycardia was present in one of these cases. In the other case, the patient had Wolff-Parkinson-White syndrome with episodes of tachycardia. Attacks of congestive heart-failure occurred in both of these cases. In one of the five cases, the patient presumably had an interatrial septal defect.

TABLE 1

CAUSES OF HEART DISEASE

CAUSE	CASES	
	Number	*Per Cent*
Arteriosclerosis	150	75.0
Infarction (91 cases)		
Angina (59 cases)		
Hypertension	30	15.0
Rheumatism	11	5.5
Syphilis	4	2.0
Miscellaneous	5	2.5
TOTAL	200	100.0

Clinical Status of Workers With Cardiac Disease

The 150 cases of arteriosclerotic heart disease deserve special consideration since they present a challenge to physician and employer. The finding that three-fourths of the patients who were disabled by cardiac disease had arteriosclerotic heart disease is not surprising since 50 per cent of the refinery workers are more than 43.8 years of age.

Table 2 shows the ages of the 200 patients at the onset of disability. Ten of the 150 patients with arteriosclerotic heart disease had diabetes, and 14 had hypertension or a past history of high blood pressure. One patient with myocardial infarction had essential hyperlipemia, and another had Buerger's disease. In less than one-fourth of the cases of myocardial infarction in which there was a clear-cut symptomatic onset, the disease first occurred during the patients' working hours.

Table 3 shows the symptoms in the different types of heart disease. Of the 91 employees with healed infarcts, 43 were essentially asymptomatic on the amount of physical activity they followed on and off the job. Fourteen complained of exertional dyspnea, and two had had episodes of frank right and left ventricular failure. Thirty-five had noted episodes of chest pain compatible with angina pectoris. This was considered mild (infrequent) in 28, and moderately severe (attacks occurring at intervals of a few days to monthly) in seven cases. Patients with severe angina were not permitted to continue at work.

In the "angina" group, attacks of chest pain occurred at infrequent intervals in 47, and at frequent intervals (every few days to monthly) in 12. Fourteen patients had had one or more definite episodes of coronary insufficiency, and 12 had had myocardial failure (predominantly left-sided in four, and both right-sided and left-sided in eight).

Fourteen of the patients with hypertensive heart disease had symptoms of congestive heart-failure, and five had angina. Four had residua of cerebral vascular accidents. In 25 cases, the hypertension was severe (Class III), and the diastolic pressure ranged from 120 mm. to 140 mm. of mercury or higher when the patients were not being treated. In the other five cases of hypertensive heart disease, the hypertension could be considered moderate (Class II), and the diastolic pressure ranged from 110 to 120 mm. of mercury. In these cases, there was roentgenologic evidence

TABLE 2

AGE OF PATIENTS AT ONSET OF DISABILITY

AGE *(Years)*	ARTERIOSCLEROTIC HEART DISEASE		HYPERTENSIVE HEART DISEASE	RHEUMATIC HEART DISEASE	SYPHILITIC HEART DISEASE	HEART DISEASE DUE TO OTHER CAUSES
	Infarcts	*Angina*				
Less than 30	0	0	0	2	0	0
30 to 39	11	4	0	1	0	0
40 to 49	23	22	7	4	0	3
50 to 59	54	28	20	4	4	2
60 to 64	3	5	3	0	0	0
TOTAL	91	59	30	11	4	5

TABLE 3

SYMPTOMS OF HEART DISEASE

TYPE OF HEART DISEASE	ANGINA			CARDIAC FAILURE	
	Mild	*Moderate*	*Severe*	*Dyspnea*	*Edema*
Arteriosclerotic (150 cases)	75	19	0	26	10
Infarction (91 cases)	28	7	0	14	2
Angina (59 cases)	47	12	0	12	8
Hypertensive (30 cases)	5	0	0	14	6
Rheumatic (11 cases)	1	0	0	4	4
Syphilitic (4 cases)	0	1	0	1	1
Other types (5 cases)					
Calcific aortic stenosis (2 cases)	1	0	0	2	0
Arrhythmia (2 cases)	0	0	0	2	2
Congenital (1 case)	0	0	0	0	0

of cardiac enlargement, and the electrocardiographic pattern was abnormal.

Four of the 11 patients with rheumatic heart disease had overt symptoms of cardiac failure. Nine had murmurs characteristic of involvement of both the mitral and the aortic valves. Three patients had a fixed rhythm of auricular fibrillation.

The four patients with syphilitic heart disease had cardiac murmurs typical of "open" aortic insufficiency and roentgenologic evidence of cardiac enlargement, but only one had had symptoms of cardiac failure. In all of the four cases, serologic tests for syphilis were positive, and the histories showed that the patients had had syphilis for a number of years before the availability of penicillin or any of the other modern methods of treatment for this condition.

The two patients with calcific aortic stenosis complained of dyspnea and weakness. One had angina and claudication, and both had evidence of left ventricular hypertrophy. Both patients with paroxysmal arrhythmia had had attacks of cardiac failure. The patient with congenital heart disease, a female clerk, was asymptomatic, but roentgenographic examination disclosed evidence of an enlarged pulmonary artery segment and suggestive evidence of enlargement of the right side of the heart. The only other female included in this study was a Negro maid who had hypertensive heart disease and cardiac failure.

Work Status of Patients With Cardiac Disease

Table 4 shows the distribution of the patients with cardiac disease among the major job classifications. Actually, we have been able to place them in all types of refinery jobs, from executive to laborer. Of the 16 patients with infarcts who were working as supervisors, 11 were in the foreman category; five were at a higher executive level. At the other end of the work scale, more than one-fourth of the entire group of patients were in the unskilled worker category (mechanical and process helpers, laborers, etc.), and nearly one-half were in the skilled worker category (composed of craftsmen of the various mechanical trades, and operators and assistant operators on refinery units). That three-fourths of the cardiac patients were able to work safely and effectively in these categories is highly significant. This is undoubtedly in part a reflection of the relatively high degree of mechanization, and of the good environmental control (presence of air-conditioned mechanical shops, control rooms, etc.) in the refinery. It is also the result of a placement program that recognizes an individual's capacities, rather than merely stressing his limitations. We have found that approximately a third of our employees with heart disease are able to continue in their previous assignments with little if any change, and that more than half are able to do the

TABLE 4

WORK CLASSIFICATION OF PATIENTS WITH HEART DISEASE

CLASSIFICATION	ARTERIOSCLEROTIC HEART DISEASE		HYPERTENSIVE HEART DISEASE	RHEUMATIC HEART DISEASE	SYPHILITIC HEART DISEASE	OTHER TYPES	TOTAL	
	Infarct	*Angina*					*Number*	*Per cent*
Supervisory	16	3	2	0	0	0	21	10.5
Technical	8	3	1	5	1	0	18	9.0
Clerical	8	4	0	1	0	1	14	7.0
Skilled	42	37	9	4	0	2	94	47.0
Unskilled	17	12	18	1	3	2	53	26.5
TOTAL	91	59	30	11	4	5	200	100.0

TABLE 5

INCIDENCE OF DISABLING HEART DISEASE AMONG 6,861 MALE EMPLOYEES OF A REFINERY

GROUP	INCIDENCE, PER CENT	
	Arteriosclerotic heart disease	*All types of heart disease*
Supervisory and administrative (765)	2.5	2.8
Technical and clerical (1,047)	2.2	2.9
Both groups (1,812)	2.3	2.9
Skilled (3,059)	2.6	3.0
Unskilled (1,990)	1.6	2.7
Both groups (5,049)	2.1	2.9
All male employees (6,861)	2.2	2.9

same job with some alteration of its required activities. The remainder (less than 20 per cent) must be assigned to a new job.

The incidence of heart disease among male employees in different job categories is rather consistent (table 5). The incidence of arteriosclerotic heart disease was 2.6 per cent among skilled workers while it was only 1.6 per cent among unskilled workers. This apparent difference would seem to be readily explained on the basis of age, since skilled workers are significantly older than unskilled workers. Consequently, we feel that no group of employees is particularly vulnerable to heart disease.

Workers with cardiac disease are effective on the job. It is noteworthy that the partially disabled employee can be properly placed with no resultant loss in effectiveness or productivity. Only four of the 200 cardiac workers were on the supervisors' list of "substandard" employees during 1956. In one of these, a machinist assigned to maintenance work on a unit, the physical disability resulting from inadequately controlled congestive failure was the cause of ineffectiveness. He received a disability retirement in early 1957. In two cases, a cardiac neurosis was a major contributory cause of "substandard" work status. The fourth case seems one of poor motivation for work.

TABLE 6

ABSENCE FROM WORK CAUSED BY 96 ATTACKS OF MYOCARDIAL INFARCTION*

MONTHS OF ABSENCE	ATTACKS
None	5
1	12
2	16
3	28
4	11
5	12
6	6
More than 7	6

*The 96 attacks occurred in 91 cases.

TABLE 7

YEARS PATIENTS WERE ABLE TO WORK WITH A CARDIAC DISABILITY

TYPE OF HEART DISEASE	YEARS WORKED		
	½ to 2	*2 to 5*	*5 or more*
Arteriosclerotic heart disease	32	71	36
Infarction	16	39	29 (Maximum was 11 yr.)
Angina	16	32	7 (Maximum was 12 yr.)
Other types	4	34	9 (Maximum was 8 yr.)

The amount of sickness absenteeism attributable to heart disease for the whole group was not high. Excluding absences which were the direct result of myocardial infarction (see below) or disability retirement, the average for each employee was only one time on "sick report" for a total of seven calendar days each year. No figures are available for a suitable control group, but this represents an absenteeism experience roughly equal to that of the average refinery worker for all medical causes. An excellent study of this subject has recently been presented by Thorpe.[10]

Table 6 shows the months of absence from work caused by 96 attacks of myocardial infarction which occurred in 91 cases of arteriosclerotic heart disease. It may seem surprising that 17 of the attacks caused an absence of only a month or less. No time was lost as a result of five of the attacks. In many cases in which little or no time was lost, the infarct was clinically "silent," and the diagnosis was made in retrospect.

In cases of uncomplicated myocardial infarction in which there is very little evidence of myocardial damage, the patient may be permitted to resume part-time work of a very light nature (clerical work, for example) after six or eight weeks of convalescence. We believe that the majority of patients with uncomplicated myocardial infarction can return to light work after three or four months. It has been our experience that patients with prolonged invalidism often are unable to return to work owing to a disabling cardiac neurosis or because of symptoms of severe angina or cardiac failure.

Table 7 shows the number of years that patients who were partially disabled by cardiac disease were able to work. The average number of years worked by each employee who has been successfully placed in an assignment six months or longer is as follows: patients with arteriosclerotic heart disease, 3.9 years; patients with arteriosclerotic heart disease and myocardial infarction, 4.3 years; patients with arteriosclerotic heart disease and angina, 3.3 years, and patients with heart disease due to other causes, 3.4 years. All those limited by heart disease have a total work experience of 702 man-years of productive employment.

Summary

By means of careful clinical evaluation, it is possible to determine the capacity of cardiac patients for work. Availability of engineering analysis of various jobs, expressed in the same capacities, permits proper placement by matching the patient's capacities with the demands of the job. Employees with partially disabling heart disease may continue to work effectively with proper placement.

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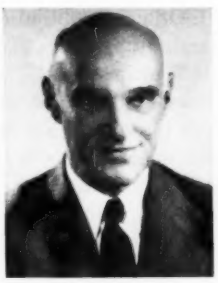
The Topical and Systemic Use of Corticosteroids in the Treatment of Skin Disease

MARION B. SULZBERGER, VICTOR H. WITTEN AND ALFRED W. KOPF*

New York University-Bellevue Medical Center, New York

THE adrenal corticosteroids and related compounds have gained an unchallenged position in dermatologic therapy. These compounds, hereinafter designated "corticosteroids," have securely established their worth more rapidly than any group before them and have had an unparalleled influence in the successful management of numerous diseases of the skin. They have kept alive patients with heretofore fatal cutaneous diseases and have made life useful and worth living for innumerable patients with certain otherwise incapacitating and torturesome dermatoses.



MARION B. SULZBERGER

VICTOR H. WITTEN

ALFRED W. KOPF

There are currently in the United States over 60 different proprietary preparations of corticosteroids available for topical use, and scarcely a month goes by without the appearance of several more. Not only is it difficult to keep up with the various external preparations, but the corticosteroids for systemic administration are also marketed under a confusing number of names and forms.

We hope that this brief report will prove

*Department of Dermatology and Syphilology, New York University-Bellevue Medical Center (Dr. Marion B. Sulzberger, Chairman); Skin and Cancer Unit, University Hospital, New York, New York.

helpful to the physician confronted by this deluge of preparations and the Babel of their accompanying names and claims. It represents our attempt to set forth simple guides to the clinical use of these compounds in managing selected skin diseases.

Topical Use of Corticosteroids

General considerations—Hydrocortisone, prednisolone and ethamicort are the corticosteroids in most widespread use for topical dermatologic therapy today. Fludrocortisone has received somewhat limited popularity because it can be absorbed percutaneously, on occasion in sufficient amounts to produce sodium retention and edema.[1,2]

As topical agents the corticosteroid preparations have many desirable attributes, including (1) great efficacy in the management of a wide variety of common dermatoses, often being rapidly effective even in small quantities;[3-7] (2) ease of use and lack of stain, stink or sting when applied to the skin; (3) no reported allergic sensitization or allergic reactions; (4) no reported untoward systemic effects attributable to percutaneous absorption (with the exception of fludrocortisone); (5) practically unlimited stability in the commonly used types of vehicles; (6) no regular increased resistance or habituation, and (7) compatibility with practically all other commonly used topical medicaments.

Corticosteroid preparations available for topical use—Table 1 outlines the corticosteroid preparations currently available for topical use. While this list may have been complete as the manuscript went to press, it will undoubtedly be incomplete by the time this report reaches its readers. Not only may the older corticosteroids appear in new vehicles, different packagings, various concentrations and different combinations, but even entirely new topically active corticosteroids may be marketed. In practice it is necessary to know a few such preparations well, including the type of vehicle in which they are incorporated, the various concentrations, the type of packaging, the presence of other active ingredients, etc. We constantly find need to refer to this compilation and therefore include it here.

Indications—Table 2 presents a list of the most common dermatoses which can in many cases be benefited by the topical use of the corticosteroids.

The combination of topical corticosteroids with antibiotics such as neomycin, bacitracin, polymyxin B, oxytetracycline, etc., may be beneficial in controlling certain dermatoses which are secondarily infected with pyogenic organisms. VIOFORM®, STEROSAN® and DIODOQUIN® provide antibacterial and antimycotic properties and have definite indications when used in combination with corticosteroids. Of course, when combinations of corticosteroids and antimicrobial agents are used, allergic eczematous contact dermatitis may occur to the latter. Therefore one should be on the lookout for possible worsening of the dermatitis at the sites of treatment, since such worsening may not necessarily represent an exacerbation of the original disease but may be an allergic reaction to the incorporated antimicrobial agent. It is important to bear in mind that the clinical features of this allergic eczematous contact dermatitis may be altered by the corticosteroid and that this may make detection and diagnosis difficult.

Other combinations with tars, quinolines and antipruritics are outlined in table 1. The indications for the use of these corticosteroid combinations are similar to the indications for the use of the substances incorporated—for example, tar in atopic dermatitis, eczematous dermatitis and seborrheic dermatitis, Vioform in nummular eczema, and so on.

Contraindications to the topical use of steroids—The steroids have thus far proved to be among the safest of all topically applied medications. This does not apply to fludrocortisone because of the aforementioned percutaneous absorption which sometimes takes place in sufficient amounts to cause fluid retention. When employing fludrocortisone we generally confine its use to limited areas of skin in adults who do not have clinical or anamnestic evidence of renal or cardiac disease. Contraindications to the topical use of steroids may include thermal burns and herpes simplex infections (certainly and especially when involving the eye). Some investigators have also

TABLE 1

PROPRIETARY CORTICOSTEROID PREPARATIONS CURRENTLY AVAILABLE FOR TOPICAL USE

PRODUCT	MANUFACTURER	CONCENTRATION OF CORTICOSTEROID (PER CENT)	OTHER ACTIVE INGREDIENTS	VEHICLE	QUANTITIES AND CONTAINERS
Group 1—Hydrocortisone only					
CORT-DOME® Creme	Dome Chemical	0.5, 1 and 2	None	Acid MANTLE® Creme	½, 1, 2, 4 and 16 oz. jars
Cort-Dome Lotion	Dome Chemical	0.5, 1 and 2	None	Acid Mantle Lotion	½, 1, 2 and 4 oz. and 1 pint plastic squeeze bottles
CORTEF® Acetate Ointment	The Upjohn Company	1 and 2.5	None	Ointment	5 and 20 gm. tubes
CORTIFAN® Cream 1%	Schering Corporation	1	None	Water-washable cream	10 gm. tube
CORTISPRAY®	Walker Laboratories, Inc.	0.5	None	Liquid	15 cc. squeeze spray bottle
CORTRIL® Acetate Topical Ointment	Pfizer Laboratories	1 and 2.5	None	Ointment	5 and 15 gm. tubes
Hydrocortisone Acetate Ointment	Bryant	1 and 2.5	None	Ointment	5 and 20 gm. tubes
HYCORTOLE® Cream	Premo	1 and 2.5	None	Cream	5 and 15 gm. tubes
Hycortole Lotion	Premo	1	None	Lotion	15 cc. bottle
Hycortole Ointment	Premo	1 and 2.5	None	Ointment	5 and 15 gm. tubes
HYDROCORTONE® Acetate	Merck Sharp & Dohme	1 and 2.5	None	Zinc stearate, polyethylene glycol, propylene glycol, water, ointment	5, 15 and 30 gm. tubes
Hydrocortone Topical Lotion	Merck Sharp & Dohme	0.5, 1 and 2.5	None	Lotion	15 cc. plastic bottle
TOPICORT® Ointment	Roussel	1 and 2.5	None	Ointment	5 and 20 gm. tubes
Topicort Spray	Roussel	0.5	None	Lotion	15 cc. aerosol spray
Group 2—Hydrocortisone plus other active agents					
Acne Cort-Dome Creme	Dome Chemical	0.25	4 per cent sulfur, 1 per cent thiobis (4, 6 dichlorophenol), 3 per cent resorcinol monoacetate	Acid Mantle Creme	1 oz. tube
Acne Cort-Dome Lotion	Dome Chemical	0.25	4 per cent sulfur, 1 per cent thiobis (4, 6 dichlorophenol), 3 per cent resorcinol monoacetate	Acid Mantle Lotion	1 oz. plastic squeeze bottle

TABLE 1 *(continued)*

PROPRIETARY CORTICOSTEROID PREPARATIONS CURRENTLY AVAILABLE FOR TOPICAL USE

PRODUCT	MANUFACTURER	CONCENTRATION OF CORTICOSTEROID (PER CENT)	OTHER ACTIVE INGREDIENTS	VEHICLE	QUANTITIES AND CONTAINERS
ACHROCORT®	Lederle Laboratories	1	3 per cent tetracycline hydrochloride	Water-washable cream	5 gm. tube
ACHROMYCIN® Ointment 3% With Hydrocortisone 2%	Lederle Laboratories	2	3 per cent tetracycline hydrochloride	Ointment	5 gm. tube
BACIMYCIN® With Hydrocortisone 1%	Walker Laboratories, Inc.	1	0.5 per cent neomycin, 500 units bacitracin per gram	Ointment	⅛ oz. tube
BUR-CORT®	Lamond	0.25, 0.5 and 1	None	Burow's emulsion	½, 1 and 2 oz. plastic bottles
CORT ACNE® Lotion	Dermik Pharmacal	0.25	8.5 per cent n-sulfanilyacetamide, 2 per cent resorcinol, 5 per cent colloidal sulfur	Flesh-colored greaseless lotion	1 oz. bottle
COR-TAR-QUIN® Creme	Dome Chemical	0.5 and 1	2 per cent solution of coal tar U.S.P., 1 per cent diiodohydroxyquinoline U.S.P.	Acid Mantle Creme	½, 1 and 4 oz. tubes
Cor-Tar-Quin Lotion	Dome Chemical	0.5 and 1	2 per cent solution of coal tar U.S.P., 1 per cent diiodohydroxyquinoline U.S.P.	Lotion	15, 30 and 120 cc. plastic bottles
CORTISPORIN® Ointment	Burroughs Wellcome & Co.	1	5000 units polymyxin B sulfate, 400 units bacitracin, 5 mg. neomycin per gram	Petrolatum	½ oz. tube
CORTOMYCIN®	Bryant	1 and 2.5	0.5 per cent neomycin sulfate	Ointment	5 and 20 gm. tubes
ES-A-CORT® Creme	Dome Chemical	0.5 and 1	56,000 I.U. estrone per ounce, 100,000 U.S.P. units vitamin A per ounce	Acid Mantle Creme	15 gm. tube
HIST-A-CORT-E®	Dome Chemical	0.5 and 1	100,000 units synthetic vitamin A and 56,000 I.U. estrone per ounce, 2 per cent pyrilamine maleate	Acid Mantle Creme	½ and 1 oz. tubes

maleate

TABLE 1 *(continued)*

PROPRIETARY CORTICOSTEROID PREPARATIONS CURRENTLY AVAILABLE FOR TOPICAL USE

PRODUCT	MANUFACTURER	CONCENTRATION OF CORTICOSTEROID (PER CENT)	OTHER ACTIVE INGREDIENTS	VEHICLE	QUANTITIES AND CONTAINERS
HYDROBALM® Cream	Merck Sharp & Dohme	0.5	3 per cent benzocaine, 0.05 per cent hexylated metacresol	Water-washable flesh-tone calamine cream	5, 15 and 30 gm. tubes
Hydrobalm 0.5% Topical Lotion	Merck Sharp & Dohme	0.5	3 per cent benzocaine, 0.05 per cent hexylated metacresol	Water-washable flesh-tone calamine lotion	15 and 30 cc. plastic bottles
HYDRODERM® Ointment	Merck Sharp & Dohme	1 and 2.5	0.35 per cent neomycin base; 1000 units zinc bacitracin per gram	Emollient base	5 and 15 gm. tubes
HYDRO-TAR®	Almay	0.5 and 1.0	5.83 per cent liquor carbonis detergens	Cream	15 gm. tube
NEO-CORT-DOME® Creme	Dome Chemical	0.5 and 1	0.5 per cent neomycin sulfate	Modified Acid Mantle Creme	5 gm. and ½, 2 and 4 oz. tubes
Neo-Cort-Dome Lotion	Dome Chemical	0.5 and 1	0.5 per cent neomycin sulfate	Acid Mantle Lotion	½, 1 and 4 oz. plastic squeeze bottles
NEO-CORTEF® Cream	The Upjohn Company	1 and 2.5	0.5 per cent neomycin sulfate	Cream	5 gm. tube
Neo-Cortef Lotion 1%	The Upjohn Company	1	0.5 per cent neomycin	Lotion	15 and 30 cc. plastic bottles
Neo-Cortef Ointment	The Upjohn Company	0.5, 1 and 2.5	0.5 per cent neomycin sulfate	Ointment	5 and 20 gm. tubes
NEOPOLYCIN®-HC Ointment	Pitman-Moore Company	1	Neomycin sulfate 3 mg., bacitracin 400 units, polymyxin B sulfate 8000 units per gram	FUZENE® Ointment	5 gm. tube
NEO-RESULIN-F®	Almay	0.5	1.5 per cent resorcinol monoacetate, 2.0 per cent sulfur, 0.5 per cent neomycin sulfate	Cream	15 gm. tube
NEO-SUPERTAH® 5	Tailby-Nason	1	Supertah (a concentrate of crude coal tar) equivalent to 5 per cent crude coal tar	Washable base	½ oz. jar

TABLE 1 *(continued)*

PROPRIETARY CORTICOSTEROID PREPARATIONS CURRENTLY AVAILABLE FOR TOPICAL USE

PRODUCT	MANUFACTURER	CONCENTRATION OF CORTICOSTEROID (PER CENT)	OTHER ACTIVE INGREDIENTS	VEHICLE	QUANTITIES AND CONTAINERS
NEO-TARCORTIN® Ointment	Reed & Carnrick	0.5	0.35 per cent neomycin sulfate, 5.0 per cent coal tar extract (TARBONIS®)	Hydrophilic vanishing cream	7 gm. and 1 oz. tubes
PANTHO-F® Cream	U. S. Vitamin Corporation	0.2 and 1	2 per cent panto-thenylol	Water-miscible cream	0.2 per cent in 5, 15 and 20 gm. and 2 oz. tubes and 1 lb. jars; 1 per cent in 5 and 20 gm. tubes
Resulin-F Cream	Almay	0.5	1.5 per cent resorcinol monoacetate, 2.0 per cent sulfur	Cream	15 gm. tube
SELSUNEF® Ointment	Abbott Laboratories	0.5	0.5 per cent selenium disulfide	Soft petrolatum	5 gm. tube
Sterosan-Hydrocortisone Ointment and Cream	Geigy Pharmaceuticals	1	3 per cent 5,7-dichloro-8-hydroxyquinaldine	Ointment or cream	5 gm. tube
TARCORTIN® Ointment	Reed & Carnrick	0.5	5.0 per cent coal tar extract	Hydrophilic vanishing cream	7 gm. and 1 oz. tubes
TERRA-CORTRIL® Ointment	Pfizer Laboratories	1	3 per cent TERRAMYCIN®	Ointment	5 and 15 gm. tubes
Vioform-Hydrocortisone Cream	Ciba Pharmaceutical Products Inc.	1	3 per cent Vioform	Cream	5 and 20 gm. tubes
Vioform-Hydrocortisone Lotion	Ciba Pharmaceutical Products Inc.	1	3 per cent Vioform	Water-washable lotion	15 cc. plastic squeeze bottle
ZETONE® Cream	Dermik Pharmacal	0.25	1 per cent ZETAR®	Vanishing cream base	1 oz. jar
Zetone Lotion	Dermik Pharmacal	0.25	1 per cent Zetar	Flesh-colored greaseless lotion	30 cc. bottle
Group 3—Prednisolone and prednisolone-21-phosphate					
HYDELTRACIN® Topical Lotion	Merck Sharp & Dohme	0.5 prednisolone	0.5 per cent neomycin	Lotion	15 cc. plastic squeeze bottle
HYDELTRASOL® Lotion	Merck Sharp & Dohme	0.5 prednisolone-21-phosphate (as sodium salt)	None	Lotion	15 cc. plastic squeeze bottle

TABLE 1 *(continued)*

PROPRIETARY CORTICOSTEROID PREPARATIONS CURRENTLY AVAILABLE FOR TOPICAL USE

PRODUCT	MANUFACTURER	CONCENTRATION OF CORTICOSTEROID (PER CENT)	OTHER ACTIVE INGREDIENTS	VEHICLE	QUANTITIES AND CONTAINERS
Hydeltrasol Ointment	Merck Sharp & Dohme	0.5 prednisolone-21-phosphate (as sodium salt)	None	Ointment	5 gm. tube
METI-DERM® Aerosol	Schering Corporation	0.3 prednisolone (a three second spray delivers approximately 0.5 mg. prednisolone)	None	Liquid	150 gm. aerosol spray can
Meti-Derm Cream	Schering Corporation	0.5 prednisolone	None	Water-washable cream	10 and 25 gm. tubes
Meti-Derm Ointment With Neomycin	Schering Corporation	0.5 prednisolone	0.5 per cent neomycin	White petrolatum	10 and 25 gm. tubes
NEO DELTA CORTEF® Lotion	The Upjohn Company	0.5 prednisolone	0.5 per cent neomycin sulfate	Lotion	15 cc. bottle
Neo Delta Cortef Ointment Topical	The Upjohn Company	0.5 prednisolone	0.5 per cent neomycin sulfate	Ointment	5 and 20 gm. tubes
NEO-HYDELTRASOL® Lotion	Merck Sharp & Dohme	0.5 prednisolone-21-phosphate (as sodium salt)	0.5 per cent neomycin sulfate	Lotion	15 cc. plastic squeeze bottle
Neo-Hydeltrasol Ointment	Merck Sharp & Dohme	0.5 prednisolone-21-phosphate (as sodium salt)	0.5 per cent neomycin sulfate	Ointment	5 gm. tube
Group 4—Fludrocortisone					
ALFLORONE® Acetate Lotion	Merck Sharp & Dohme	0.1 and 0.25	None	Lotion	15 cc. plastic bottle
Alflorone Acetate Ointment	Merck Sharp & Dohme	0.1 and 0.25	None	Emollient base	5 and 15 gm. tubes
F-CORTEF® Ointment	The Upjohn Company	0.1 and 0.2	None	Ointment	5 gm. tube
FLORINEF® Lotion	E. R. Squibb & Sons	0.05, 1 and 0.2	None	Lotion	15 cc. plastic squeeze bottle
Florinef Ointment	E. R. Squibb & Sons	0.1 and 0.2	None	PLASTIBASE®	5 and 20 gm. tubes
Florinef-S Cream	E. R. Squibb & Sons	0.1	0.25 per cent neomycin, 0.025 per cent gramicidin	Cream	5 gm. tube
Florinef-S Lotion	E. R. Squibb & Sons	0.05 and 0.1	0.25 per cent neomycin, 0.025 per cent gramicidin	Lotion	15 cc. plastic squeeze bottle

TABLE 1 *(continued)*

PROPRIETARY CORTICOSTEROID PREPARATIONS CURRENTLY AVAILABLE FOR TOPICAL USE

PRODUCT	MANUFACTURER	CONCENTRATION OF CORTICOSTEROID (PER CENT)	OTHER ACTIVE INGREDIENTS	VEHICLE	QUANTITIES AND CONTAINERS
Florinef-S Ointment	E. R. Squibb & Sons	0.1	0.25 per cent neomycin, 0.025 per cent gramicidin	Plastibase	5 and 20 gm. tubes
MYCONEF® Ointment	E. R. Squibb & Sons	0.1	0.25 per cent neomycin, 0.025 per cent gramicidin, 100,000 units nystatin per gram	Plastibase	15 gm. tube
Group 5—Hydrocortamate (hydrocortisone ethamate hydrochloride)					
MAGNACORT® Topical Ointment	Pfizer Laboratories	0.5	None	Ointment	⅛ and ½ oz. tubes
NEO-MAGNACORT® Topical Ointment	Pfizer Laboratories	0.5	0.5 per cent neomycin sulfate	Ointment	⅛ and ½ oz. tubes

TABLE 2

DERMATOSES BENEFITED BY THE TOPICAL APPLICATION OF CORTICOSTEROIDS

Allergic eczematous contact-type dermatitis
Anogenital pruritus
Atopic dermatitis (including infantile eczema)
Dermatitis (e.g., "idiopathic," contact or atopic) of eyelids and peribuccal areas
Distinctive exudative discoid and lichenoid chronic dermatosis (Sulzberger and Garbe) (except in certain areas, e.g., penis, not nearly as effective as systemic administration)
Eczema of nipples and areolae
Exfoliative erythrodermas (some forms and areas)
Hand dermatitis (e.g., primary irritant, "housewife's" eczema)
Intertrigo (inflammatory)
Lichen simplex chronicus
Nummular eczema
Otitis externa
Psoriasiform dermatitis (some forms, especially of anogenital and intertriginous areas)
Seborrheic dermatitis (particularly of face)
Miscellaneous eczematized and pruritic dermatoses

considered pyodermas to be contraindications to the topical use of the corticosteroids, but we have not seen clear-cut worsening of bacterial skin infections resulting from the application of these preparations. In the presence of bacterial infections superimposed on an underlying dermatitis it is, of course, logical to use antiseptics or antibiotics separately or in combination with the topical corticosteroids.

Optimal concentrations of corticosteroids for topical use—There is now general agreement that the optimal concentrations of the corticosteroids for topical use are as follows:

Hydrocortisone, 1.0 to 2.5 and, exceptionally, 5.0 per cent.

Fludrocortisone, 0.1 to 0.25 per cent.

Hydrocortamate, 0.5 per cent.

Prednisolone, 0.5 to 1 per cent.

In our hands no remarkable therapeutic difference has been noted between the free alcohol and esters of these compounds. Although some therapeutic superiority has been claimed for the topical applications of certain corticosteroids,[3, 8, 9] the over-all response to the various corticosteroids under consideration appears to be quite comparable when optimal concentrations of each are used in the same manner of application. On occasion ex-

ceptions are noted in which a dermatosis will respond to the topical applications of one corticosteroid better than to the applications of another.

Topical application of corticosteroids—Table 1 illustrates the complexity of pharmaceutical formulation. The choice of the vehicle in which the corticosteroid is incorporated can be of considerable importance in the successful management of certain dermatoses. The selection depends to a great measure on the stage of the eruption (acute, subacute or chronic), on whether it is wet or dry, scaly or lichenified, on the extent and the sites involved, and so forth. The patient himself can often help in selecting the vehicle; in particular those with chronic dermatoses usually know the type of vehicle (lotion, ointment, cream) which they tolerate best.

In general, acute or moist eruptions and those involving the scalp and intertriginous areas tolerate lotions and water-miscible creams better, whereas eruptions of less acute nature and those which are dry and scaly do better with greasy ointments.

Because of their relatively high cost, these preparations are as a rule applied sparingly. It is fortunate that they are usually extremely effective even in small amounts, provided they cover the involved areas adequately and *are inuncted well.* In most cases two or three applications daily are required initially. Once the dermatosis has improved, the frequency of the applications may be reduced gradually. Should the eruption disappear completely, the frequency of application can be gradually reduced and finally the applications discontinued altogether. In this way the maintenance dose may be ascertained. It is necessary for some patients to repeat applications every third or fourth day for prolonged periods—for example, to keep pruritus ani under control.

The prolonged and regular topical use of corticosteroids (fludrocortisone excepted), even on widespread areas of dermatitis, has proved safe in our experience. Some patients with large areas of affected skin (e.g., erythroderma, atopic dermatitis) have used these compounds steadily for over five years without clinical evidence of systemic absorption.

Intralesional injection of corticosteroids—The administration of corticosteroids by injection directly into the lesion has been beneficial in a limited number of cutaneous diseases, among which are alopecia areata,[10,11] hypertrophic lichen planus,[12] perhaps also keloids, certain areas of lichenified dermatitis and circumscribed lichen simplex, and certain resistant plaques of psoriasis. Our experience has been limited to injections of hydrocortisone. Hydrocortone Acetate Suspension (Merck Sharp & Dohme), 25 mg. per milliliter of diluent, is injected intracutaneously or subcutaneously or into the lesion with a fine needle (24 or 26 gauge) and a tuberculin syringe.* Usually, local anesthesia is not required. It is too early to evaluate the ultimate success or failure of this mode of administration but the results seem promising, particularly in circumscribed patches of alopecia areata and hypertrophic lichen planus.

Systemic Administration of Corticosteroids

General considerations—Cortisone and hydrocortisone and their delta analogues prednisone and prednisolone, respectively, are the corticosteroids which are commonly used systemically in dermatologic practice. Fludrocortisone is not used in the systemic therapy of skin diseases because of its marked effect on electrolyte balance and water metabolism and the severe water retention which is associated. New steroids such as methylprednisolone (6-methyl-delta-1-hydrocortisone), MEDROL®, The Upjohn Company, and triamcinolone (delta 1, 9 alpha-fluro, 16 alpha-hydroxy, hydrocortisone), ARISTOCORT®, the Lederle Laboratories, and KENACORT®, E. R. Squibb & Sons, are now under investigation.

While our experience with these two steroids is much more limited than with the older compounds of this series, certain things can be said on the basis of our limited studies. Triamcinolone, milligram for milligram, seems to be somewhat more effective than other members of the series in its morbidistatic effect on

*For this same purpose, we have recently begun to use a suspension of 200 mg. hydrocortisone acetate (Cortef Acetate, The Upjohn Company) per milliliter of diluent.

TABLE 3*

INDICATIONS FOR SYSTEMIC CORTICOSTEROID THERAPY

Very severe refractory cases of ordinarily self-limited acute dermatoses in which corticosteroids given for short periods are often effective as morbidistatic agents:

1. Eczematous contact-type dermatitis
2. Acute urticaria and angioneurotic edema
3. Certain drug eruptions (e.g., urticarial, purpuric, bullous)
4. Erythema multiforme

Very severe refractory cases of ordinarily nonfatal, persistent chronic or recurrent dermatoses in which corticosteroids given over prolonged periods may be effective morbidistatic agents:

1. Atopic dermatitis (including infantile eczema)
2. Exfoliative erythrodermas
3. Nummular eczema
4. Eczematous or pustular eruptions of the hands
5. Distinctive exudative discoid and lichenoid chronic dermatosis (Sulzberger and Garbe)
6. Chronic urticaria
7. Seborrheic dermatitis, particularly when widespread and in intertriginous areas
8. Incapacitating widespread or exanthematous psoriasis, when proved refractory to other measures inclusive of selected forms of radiation therapy

Ordinarily fatal dermatoses in which corticosteroids are often effective as morbidistatic agents:

1. Pemphigus (all forms)
2. Acute and subacute systemic lupus erythematosus
3. Acute phases of dermatomyositis

*From Sulzberger and Witten.[15]

TABLE 4

COMPLICATIONS OF SYSTEMIC CORTICOSTEROID THERAPY

Major

- Adrenal insufficiency
- Compression and other pathologic fractures
- Hypertension (when marked)
- Osteoporosis (vertebral, hip, etc.)
- Peptic ulcer
- Psychoses (manic, depressive, etc.)
- Systemic intercurrent infection (tuberculosis, septicemia, disseminated chickenpox, etc.)
- Thromboses
- Uncontrolled diabetes
- Uremia

Minor

- Acneiform lesions
- Hirsutism
- Hypothyroidism
- Increased appetite
- Mild glycosuria or hypertension or both
- Mild psychic changes (irritability, euphoria, restlessness, insomnia, etc.)
- Pedal edema
- Petechial and purpuric skin lesions
- Regional "fat" distribution (moon facies, buffalo hump, supraclavicular fat pads, etc.)
- Tremors and paresthesias

dermatoses such as psoriasis and perhaps also certain eczematous and eczematoid eruptions and atopic dermatitis. Methylprednisolone, while in some cases equal to or even superior to triamcinolone, is generally milligram for milligram not quite as effective as the latter in its morbidistatic action in the dermatoses mentioned.

It is still much too early to draw any definite conclusions on the frequency and nature of the undesirable effects of these newer corticosteroids. Nevertheless, it would seem that muscle weakness appears in a larger proportion of patients receiving triamcinolone than in those receiving other corticosteroids we have used, including methylprednisolone. Another undesirable and indeed sometimes dangerous effect from triamcinolone has been reported;[13] this is muscle wasting, particularly of certain extremity muscles.

The aforementioned tentative impressions on the effectiveness of these newer hormones, together with our more detailed experience with the older corticosteroids, make it clear that it is by no means certain just which will be best for a particular patient. Individualization in the selection of therapy is still the only proper approach and is one that requires a great deal of judgment and careful observation of the particular patient's reaction and the response of the dermatosis.

Because of the ease with which these compounds may be taken orally, this being ideal for ambulatory therapy, no other form of administration will be discussed.

Ordinarily there is no difference in the response of a dermatosis to any of the four corticosteroids under consideration. In rare instances one of the corticosteroids will prove more beneficial than another. Such a possibility should be kept in mind generally when an eruption which commonly responds to the corticosteroids fails to improve satisfactorily to what ordinarily would be considered an adequate dose.

Judging from the course of the dermatoses which are treated with these compounds, the corticosteroids are not curative but rather suppress the clinical manifestations, an effect which one of us (M. B. S.[14]) has termed "mor-

bidisiatic." For this reason, when a corticosteroid is completely withdrawn, a prompt flare-up of the disease under treatment may occur. Of course this does not occur in those dermatoses which have a self-limited course and which are to all practical purposes "cured" when corticosteroids are continued long enough to permit the disease to run its course to spontaneous termination.

When the corticosteroids are employed systemically in the management of dermatologic conditions the following major factors must be taken into consideration.

1. Does the disease represent an indication for their use?
2. Are there contraindications to their use?
3. Can and will the patient remain under constant medical supervision while receiving these medicaments?

Indications for the systemic use of corticosteroids—The most important and frequently encountered dermatologic indications for the administration of oral corticosteroid therapy are presented in table 3.

Contraindications—It is mandatory that the physician consider all the findings of the history and physical examination before beginning therapy. The main attention should be focused on tuberculosis, diabetes, heart disease, hypertension, renal disease, mental disturbances (institutionalization, psychiatric care), thrombotic episodes, gastrointestinal disturbances (particularly in relation to peptic ulcer), chronic focal infections and osteoporosis or recent fractures. As a result of the increasing knowledge concerning the systemic use of the corticosteroids, a history or presence of one or more of these conditions is no longer an obligatory contraindication to the use of a selected corticosteroid. Provided the necessary medical precautions are taken, and provided the patient can be followed carefully and observed frequently, these compounds usually can be administered even for prolonged periods without prohibitive side effects.

Relative therapeutic equivalent doses of the various corticosteroids—In this era of rapidly increasing numbers of new proprietary medications, in which it is impossible to keep up one's acquaintance with the strength of the various tablets, capsules, and so on, it is fortunate that the manufacturers have dosed the different corticosteroid tablets based on their relative therapeutic effectiveness as compared with cortisone: 25 mg. cortisone acetate = 20 mg. hydrocortisone = 5 mg. prednisone or 5 mg. prednisolone.*

This means that one full-strength tablet of prednisone or prednisolone is equivalent to one full-strength tablet of hydrocortisone or to one full-strength tablet of cortisone.†

Ill effects of corticosteroids—The incidence and type of ill effects (table 4) vary with the individual patient and with the particular corticosteroid being used. In general, prednisone and prednisolone have less tendency to alter electrolyte balance and to produce fluid retention but have a somewhat greater tendency to cause or aggravate gastrointestinal complaints; whereas cortisone and hydrocortisone have distinctly greater effect on sodium and water retention but a somewhat lesser risk of producing gastrointestinal disorders.

It is our *distinct clinical impression that there is more tendency toward rounding of the face, supraclavicular and suprasternal notch "fat" pads and "buffalo hump" from the delta compounds (prednisone and prednisolone) than from equivalent therapeutic doses of cortisone or hydrocortisone.*

Short-term systemic corticosteroid therapy—We arbitrarily apply the designation short-term therapy with corticosteroids to any period of administration lasting less than approximately two months.[16] This would include the usual period of therapy for such dermatoses as acute contact dermatitis (e.g., poison ivy), acute allergic drug eruption (e.g., penicillin), acute urticaria, severe flare-ups of chronic dermatoses, etc.

The size of the initial effective dosage de-

*While it is too early to be sure, at present it seems that, in their effects in most dermatoses, 4.0 mg. of methylprednisolone and 3.0 to 4.0 mg. of triamcinolone correspond in therapeutic efficacy to about 25 mg. of cortisone acetate.

†Throughout the remainder of this paper we will refer to cortisone acetate dosages only. It should be assumed that any of the systemic corticosteroids may be selected and used in the proper and equivalent dose as given here.

pends on the diagnosis, stage of the disease, severity of symptoms, existing complications and contraindications, and, when possible to ascertain, the patient's previous response to the drug.

There are two schools of thought concerning the best method for establishing the effective dosage of corticosteroids. One advocates beginning with low doses and gradually increasing the daily dosage until the dermatosis is brought under control. The other school believes in starting with doses perhaps somewhat higher than are necessary and then gradually reducing the daily dosage until the lowest effective one is reached. Although on occasion (for example, in cardiac or diabetic patients) we use the "initial low dosage technic," most of our patients are started on the "initial high dosage technic." In our opinion this technic allows for more rapid control and relief of the signs and symptoms, resulting in immediate encouragement and better "patient cooperation." When the patient is followed carefully this technic does not produce an increased incidence of undesired side effects.

Fortunately, in the short-term use of these steroids undesirable effects are much less common than during prolonged administration (see below). Complications can be avoided to a great extent by close observation of the patient and careful consideration of the existing contraindications. The most common complications during short-term corticosteroid therapy are weight gain, hypertension, glycosuria, edema, general weakness, activation of peptic ulcer, psychiatric disturbances (restlessness, insomnia, anxiety, euphoria or depression), and increased appetite.

Prolonged corticosteroid therapy—In certain chronic dermatoses the prolonged continuous or intermittent use of the corticosteroids is indicated. This may be because the disease is ordinarily fatal and the steroids are lifesaving, or because the cutaneous disorder is so crippling, physically or emotionally or both, that it is justifiable to take the risks associated with long-term corticosteroid therapy.

The dosage must be "individualized" to meet the needs of the patient. Patients with severe and acute disease (pemphigus, acute disseminated lupus erythematosus, acute dermatomyositis, etc.) generally require a high initial daily dosage of 300 to 1000 mg. of cortisone in divided doses. Hospitalization is advisable during the early phases when such large dosages of steroids are given.

TABLE 5

AVERAGE SCHEDULE OF CORTISONE REDUCTION

PATIENT RECEIVING (MILLIGRAMS CORTISONE DAILY)	MAY HAVE DOSAGE REDUCED BY (MILLIGRAMS EACH TIME)
500 or more	50
100 to 500	25 to 50
25 to 100	12.5
0 to 25	2.5 to 5

As soon as feasible these high dosages should be lowered. While there can be no strict rule concerning the amount by which the cortisone dosage may be reduced each time, table 5 may be of some help in determining the steps by which the dose may be decreased in most cases.

In long-term therapy the rate at which the dosage can be reduced safely without troublesome flare-up of the dermatosis is an individual matter. When higher dosages are being administered (above 500 mg. cortisone daily), they usually can be reduced every three to seven days; whereas intervals of one, two or more weeks are often required when lower dosages (say, below 100 mg. cortisone daily) are being administered.

It has been our experience that most patients can be safely maintained on the steroids for months and even years (some of our patients now *up to seven years*) on maintenance dosages of 100 mg. or less of cortisone daily. Most complications have occurred in those patients receiving over 125 mg. cortisone daily.

Exacerbations of the dermatoses may be due to inadequate dosage, intermittent stress or the "natural cycle" of the disease. When they occur it is necessary to increase the dosage of the corticosteroid to the next higher previously effective level. Exacerbations can be so severe as to require a considerably higher dosage, but rarely one higher than the initial dosage. When the flare-up has been

TABLE 6*

PRINCIPAL MEASURES TO BE INSTITUTED FOR PATIENTS RECEIVING SYSTEMIC CORTICOSTEROID THERAPY

Examinations before instituting therapy: Complete history and studies with special reference to diabetes, hypertension, thrombotic or hemorrhagic states, psychoses, tuberculosis or other occult infection, and peptic ulcer.
Weekly or biweekly examinations during therapy: Weight, blood pressure, urinalysis, and evaluation of course of disease, general symptoms, physical and psychic state.
Special examinations when indicated: Blood counts, including circulating eosinophils; bleeding and clotting factors; "blood chemistry" for serum sodium, potassium, blood sugar, etc.; electrocardiograms; roentgenograms of osseous structures (especially vertebral column and hip); tests for thyroid function.
Procedures to prevent or manage complications: Low salt, high protein diet with potassium supplement; antacids and anticholinergics when peptic ulcer is suspected; when indicated, antibiotics, antituberculosis agents, thyroid, insulin, testosterone and other anabolic agents, diuretics, etc.

*Adapted from Sulzberger.[11]

brought under control by the increased dosage, gradual reduction should again be attempted. In most instances the dosage necessary just to control the disease (maintenance dosage) steadily declines with the passage of time. Therefore every effort should be made to reduce the dosage to the lowest possible level and keep it at each new level only as long as absolutely necessary. The maintenance dosage that we use is not necessarily that which clears up the lesions completely, but rather it is the commonly much lower and much safer amount which just suffices to keep the patient reasonably comfortable and able to carry on his normal functions. Of course the eventual goal is to discontinue the steroid altogether as soon as this is possible.

Intermittent adrenocorticotropin (ACTH) therapy has been advocated in the attempt to prevent or lessen adrenocortical depression or atrophy during long-term corticosteroid administration. We have not been convinced of the need or of the efficaciousness of this routine and therefore have not prescribed it for most of our patients.* None of our patients who has been taken off long-term corticosteroid therapy has suffered adrenal failure.† In our practice the low incidence of postcorticosteroid adrenal insufficiency may be attributed to the *very* gradual lowering of the dosage over prolonged periods, allowing for the restitution of adrenal cortex activity, and to the rather low average age and active ambulatory status of most of our patients.

Table 4 outlines some of the more common complications of systemic corticosteroid therapy. There is no substitute for constant medical supervision to permit the physician to evaluate closely the clinical response of the dermatosis and to be familiar with arising complications.

Table 6 indicates certain "routines" suggested for patients receiving systemic corticosteroid therapy.

Fortunately, patients on prolonged systemic corticosteroid therapy do not develop "addiction" to these drugs. Actually the contrary is the case, and the average patient will request that the dosage be lowered as much and as soon as possible, even when knowing that mild exacerbations may occur. On the other hand, it is true that although this mode of therapy does not produce psychic "dependence," addiction or habituation, a degree of temporary physical "dependence" (adrenal insufficiency) does develop. These differences must be clearly explained to the patient and the importance of following precise dosage instructions stressed repeatedly.

When the corticosteroids are administered as a lifesaving measure it is necessary to proceed with their use even in the face of serious contraindications and complications. Management of these complications may require the combined efforts of the general practitioner or family physician, internist, surgeon, radiologist, endocrinologist, psychiatrist and dermatologist. Through this teamwork great odds

*And they have fared as well as the few of our own patients who received periodic ACTH or those who were treated that way routinely by other physicians.

†Several, however, have felt fatigued, and these were benefited by twice-weekly injections of ACTH (20 to 40 units of the gel) given for three to four weeks.

can be overcome and serious ill effects generally obviated or successfully managed when they arise.

Summary

Topical corticosteroid therapy holds an unchallenged position of value in the management of many common skin diseases. These effective, easily used, agreeable and, to date, eminently safe steroid compounds have found widespread use in a broad spectrum of common dermatoses.

Systemic corticosteroid therapy has prolonged life, not to say saved it, for many patients with certain hitherto fatal dermatoses. It has made life again worthwhile for many who have other cutaneous diseases which, while not fatal, are ordinarily physically crippling and emotionally incapacitating.

Indications and contraindications for the topical and systemic administration of the corticosteroids are set forth in detail. Special problems relating to short-term and long-term systemic corticosteroid therapy are discussed.

It is emphasized that the physician's constant understanding and supervision are required to manage patients receiving systemic corticosteroid therapy, for without conscientious and regular medical examinations serious sequelae may arise from the injudicious or indiscriminate systemic use of these potent compounds.

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Clinicopathologic Correlation of Dysfunctional Uterine Bleeding

IRVING ROTHCHILD*

Western Reserve University School of Medicine, Cleveland

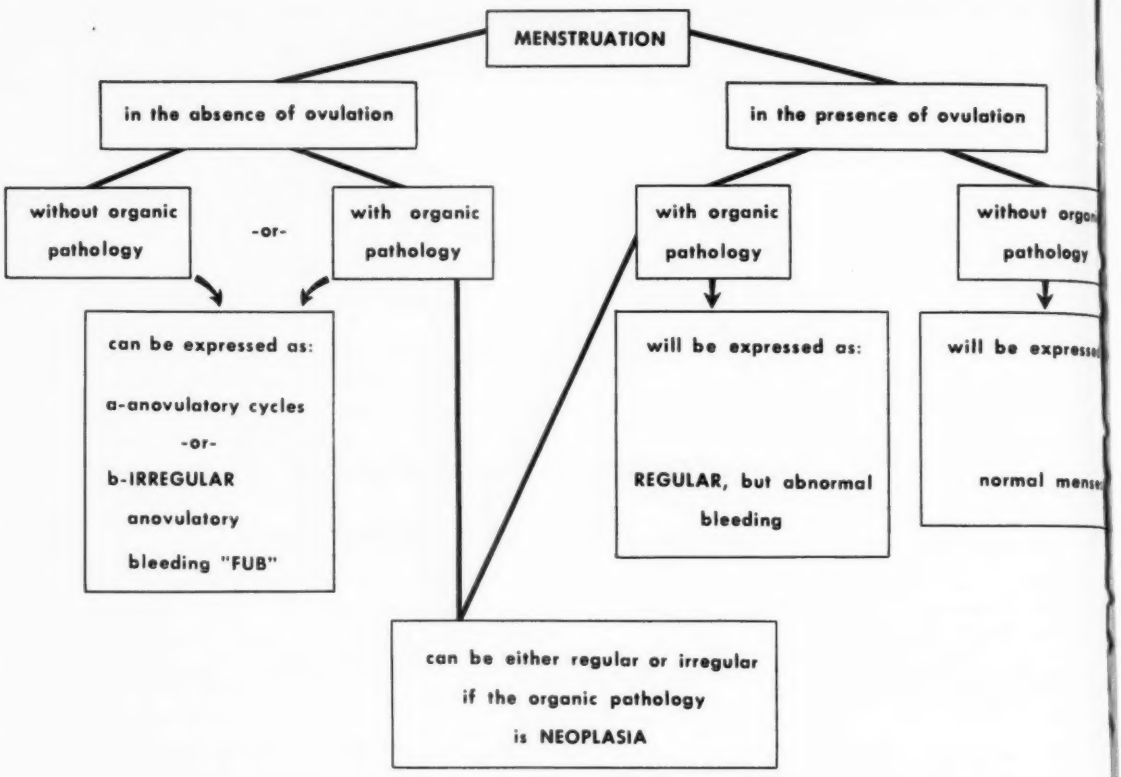
IRVING ROTHCHILD

THE term "dysfunctional uterine bleeding," or its synonym "functional uterine bleeding," means so many different things to so many different people that it serves more to perpetuate some serious errors than to have any real usefulness in the management of abnormal uterine bleeding. Either term means literally that a *functional* disturbance is the cause of abnormal bleeding. To explain this still another way, then (since disturbed function must be associated with a pathologic condition, whether we can see it or not), these terms mean that the abnormal bleeding occurs in the absence of any *demonstrable* pathologic process. Because the uterus is relatively accessible to examination and pathologic study, while the ovaries and pituitary are not, these terms, therefore, also mean that the abnormal bleeding is due to some change from the normal hormonal control over menstruation, but not to a change in the uterus itself, since demonstrable disease in the uterus would immediately make the diagnosis of functional bleeding untenable. The only logical conclusion that follows these premises is that functional uterine bleeding means irregular menstruation which results from failure of ovulation.

This would occasion no problem if the term were used for this condition alone. Too often, however, it is applied indiscriminately to any patient whose menstrual bleeding is abnormal, apparently with the mistaken assumption that any variety of excess menstruation is functional bleeding regardless of its regularity or otherwise. At best, this assumption is made

*Department of Obstetrics and Gynecology, Western Reserve University School of Medicine, Cleveland, Ohio.

Adapted from a presentation at the course in Advances in Obstetric Care and Gynecologic Bleeding at The Cleveland Clinic Foundation.



THE RELATIONSHIP BETWEEN UTERINE BLEEDING, OVULATION, AND ORGANIC REPRODUCTIVE TRACT PATHOLOGY

FIGURE 1. A diagrammatic representation of the way in which menstrual abnormalities may be related to the presence or absence of ovulation, or reproductive tract pathology.

with the additional one, "until proved otherwise"; at worst, it has led to the treatment for functional bleeding of patients with cervical or endometrial neoplasm. A brilliantly uniform lack of success has always been associated with this assumption. In this too frequent misuse of the term there is thus the danger inherent in any faulty thought process, namely, that the wrong conclusions will be reached.

To a large extent, the fault is in the term itself. It does not specifically designate the failure of ovulation as the cause of the abnormal bleeding, and by incorporating into it the word *functional*, it perpetuates the erroneous belief that causes other than anovulation, in the absence of organic disease, may produce abnormal bleeding.* If I could have my way, I would altogether abandon the use of the term dysfunctional (or functional) uterine bleeding, and for it substitute a much more descriptive one, *irregular anovulatory bleeding*, since this describes both the cause and the most outstanding clinical manifestation of the condition. But before this label can be attached to any patient, the physician's only proper diagnostic orientation should be toward abnormal uterine bleeding. When he is so oriented he must of necessity think of the many other causes besides anovulation that

*See paragraph headed "Is there a form of functional bleeding associated with ovulation?"

can produce abnormal bleeding. Only when these have been ruled out and a positive diagnosis of anovulation made, will he be justified in using this term and in instituting the proper treatment for the condition.

There are a few simple and logical guides to the proper diagnosis of anovulatory bleeding, and this paper's primary purpose is to point these out.

Abnormal Uterine Bleeding, Ovulation and Reproductive Tract Pathology

Abnormal uterine bleeding, signifying only the presence of an abnormal, excessive bleeding pattern, may be caused by or associated with cancer, fibroids, polyps, ectopic pregnancy or thyroid dysfunction, to mention just a few common causes—or by anovulation. It is implied in the term "menstrual irregularity," but this, too, is misleading. The most important single feature of the bleeding abnormality that distinguishes anovulation from most other causes is that anovulatory uterine bleeding is practically always highly irregular, while the bleeding associated with other causes, in the presence of ovulation, is just as often regular. In other words, the bleeding abnormality may occur in either a regular or an irregular pattern. If the pattern is regular, the probability is great that this is associated with ovulation and that the abnormality, therefore, is due to or associated with some organic disease in the reproductive system, or elsewhere. If the pattern is irregular, it is probably due to anovulation.

The diagram in figure 1 attempts to show how menstruation will be affected by ovulation or its absence, in the presence or absence of some pathologic condition in the reproductive tract.

In the absence of ovulation and disease in the reproductive tract, menstruation will occur either in the form of cycles of somewhat irregular length but of relatively normal duration (anovulatory cycles), or as completely irregular bleeding without a discernible pattern. The latter is what I choose to call "anovulatory irregular bleeding." There may be various gradations between these or even between these and amenorrhea. In fact, it is not unusual for a patient with anovulation to alternate between periods of amenorrhea and periods of irregular and excessive bleeding. The outstanding effect of anovulation on menstrual bleeding is thus the irregularity of the bleeding pattern. I can compare this best of all with the "irregular irregularity" of auricular fibrillation. The irregularity of anovulatory bleeding is as different from the regularity of other forms of abnormal menstrual bleeding as is that of auricular fibrillation from the fairly regular patterns of sinus tachycardia, premature ventricular or auricular systole, pulsus alternans, two to one heart-block, etc.

Organic disease may, of course, coexist with anovulation, but it will not alter the basic irregularity of anovulatory bleeding. This makes it more difficult to suspect but no more difficult to diagnose, once suspected, than when it occurs in association with ovulatory menstruation.

In contrast to this, ovulation by its very nature produces a regular pattern of menstrual flow. When no organic disease is present in the reproductive tract, there will be no abnormality in menstrual flow. Organic reproductive tract disease of the kind that produces bleeding will, in the presence of ovulation, lead to an abnormality of menstrual flow, but this abnormality will have a regular pattern.

The same general principle applies to pathologic conditions outside the reproductive tract, if they are of the kind that may affect uterine bleeding and if they exist together with ovulation. The most important of these is thyroid dysfunction, since, for reasons that are still not well understood, both hypothyroidism and hyperthyroidism can be associated with excessive menstruation (as well as with amenorrhea). However, as long as the thyroid disorder does not interfere with ovulation (which is rare), the abnormal menses will still tend to show a regular pattern.

This is the most outstanding difference between true anovulatory irregular bleeding (dysfunctional uterine bleeding) and the excess bleeding due to something like a submucous fibroid, a cervical or endometrial polyp, or, in general, any cause of uterine bleeding

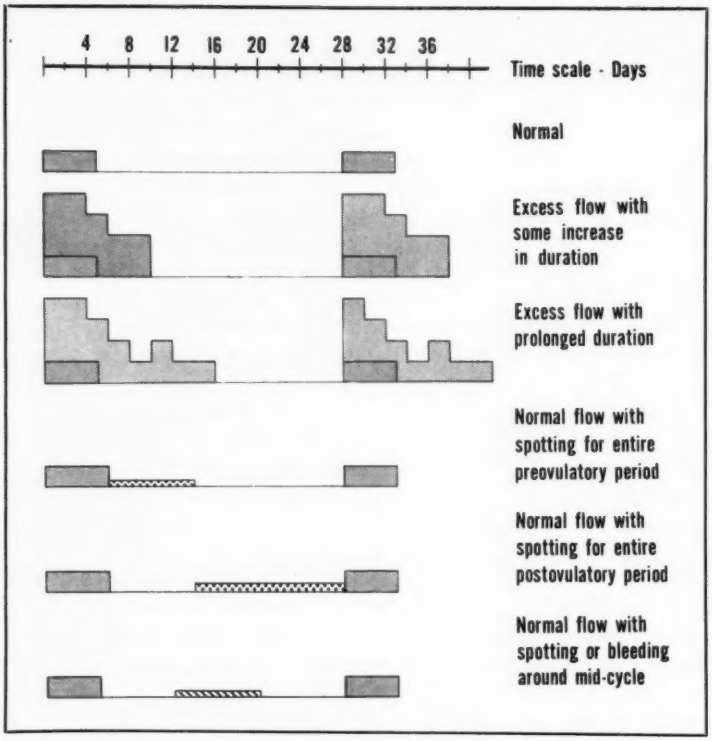

4 8 12 16 20 24 28 32 36
Time scale - Days
Normal
Excess flow with some increase in duration
Excess flow with prolonged duration
Normal flow with spotting for entire preovulatory period
Normal flow with spotting for entire postovulatory period
Normal flow with spotting or bleeding around mid-cycle

FIGURE 2. Patterns of regular menstrual abnormalities, usually associated with benign organic lesions of the reproductive tract when ovulation is present. These schematic representations of actual menstrual histories demonstrate only the more frequently seen departures from normal. The three types of excess bleeding shown in the three lower diagrams could also be described as bleeding of enough intensity to require a pad or be associated with excess bleeding during the normal period, or both. Bleeding of daily increasing severity may also occur regularly, but is not shown in this diagram.

associated with ovulation. Anovulatory bleeding, for reasons I will enlarge on shortly, is by its very nature irregular; the bleeding due to organic disease is per se neither regular nor irregular. When it occurs in the patient who ovulates regularly, this abnormality is superimposed on the regular menstruation that practically always occurs with ovulatory cycles, so that the total pattern of bleeding, no matter how abnormal, is regular also.

Let me put this another way. Abnormal excess bleeding that follows a definitely regular pattern strongly suggests the coexistence of ovulation. Ovulation is relatively easy to diagnose, and once its occurrence has been proved it (1) rules out the diagnosis of anovulatory irregular bleeding, and (2) points strongly to the presence of an organic cause for the abnormality. Regular abnormal bleeding does not by itself make the diagnosis of a pathologic condition, but serves only to heighten one's awareness of its possible existence. It should therefore prompt one to take the necessary steps to prove it.

This simple relationship would not have to be pointed out at all if errors in diagnosis did not so often lead to the incorrect treatment of patients whose bleeding pattern has demonstrated enough regularity to arouse the suspicion of ovulation and therefore of disease. In figure 2 are shown a series of schematized menstrual abnormalities. Each of these has a regular pattern, each represents the actual pattern of at least one patient I have seen; each patient previously had been diagnosed as a functional bleeder, and each was found to have had organic disease within the reproductive tract underlying the abnormal bleeding.

Reproductive tract cancer as a cause for abnormal bleeding—Before discussing the basis for the differences between anovulatory and ovulatory abnormal bleeding, I would like to emphasize that abnormal bleeding due to cancer can show any pattern and that can-

cer of the reproductive tract can occur with or without ovulation. What I have already said and what I will say, therefore, about the importance of irregularity of menstrual flow as a diagnostic aid applies only to the patient in whom every step has first been taken to rule out cancer as the cause for her abnormal bleeding.

Differences Between Anovulatory and Ovulatory Abnormal Bleeding

The point I have tried to make is that the pattern of abnormal bleeding helps to differentiate between so-called functional, or anovulatory, bleeding and the bleeding due to or associated with organic disease. I would like to add a word or two of explanation to this.

The pathologic conditions, aside from cancer, most frequently associated with abnormal uterine bleeding are fibroids, particularly the submucous variety, and endometrial or cervical polyps. There is no satisfactory explanation for the very frequent association between these conditions and abnormal bleeding, but there seems to be no doubt that such growths are influenced by ovarian hormones. Since these growths can either bleed themselves or produce endometrial bleeding, and since they are influenced by the ovarian hormones, it is not difficult to see that in the presence of an ovulatory rhythm, this abnormal bleeding must tend to be regular also. This regularity is due to the nature of the ovulation cycle itself, since each of the principal hormones of the ovary, estrogen and progesterone, is secreted cyclically, and each influences and controls periodicity of secretion of the other through its effects on the secretion of the pituitary's gonadotropic hormones. Therefore, as long as ovulation occurs, it tends to occur regularly, and the pattern of bleeding associated with it also must be regular. The variations in pattern, however, may be great (figure 2), and this is undoubtedly a function of the specific character of the organic lesion.

Irregularity, on the other hand, is the outstanding characteristic of anovulatory bleeding. The reason for this is also not difficult to see. In anovulation associated with irregular bleeding there is less interference with the cycles of follicular growth than with the ability to ovulate; the absence of ovulation and of the resulting corpus luteum deprives the organism of the important pituitary-regulating effects of progesterone. As a result, the growth cycles of the follicles tend to be both prolonged and irregular, and they alternate or are combined with irregular cycles of follicular atresia. Estrogen secretion, which in general goes on concomitantly with follicular growth, is thus both prolonged and irregular, too, and produces a more sustained stimulation of endometrial growth than occurs in the normal cycle. In many of these patients endometrial hyperplasia results, while the fluctuations in estrogen level, which to begin with are irregular, act to induce bleeding more easily from this hyperplastic tissue than from the normal endometrium. The combinations, then, of ovulation failure, irregular cycles of follicular growth and atresia, irregular but prolonged secretion of estrogens, and a hypersensitive endometrium can result in nothing but totally irregular bleeding.

Is there a form of functional bleeding associated with ovulation?—There is a widely held belief, continued by practically all textbooks of gynecology, that about 15 per cent of functional bleeders show a secretory endometrium. This implies that a kind of physiologic disturbance of menstruation—that is, one not associated with reproductive tract disease—may occur in the presence of ovulation. I believe that this is a contradiction, and would even go so far as to add that abnormal menstrual bleeding cannot take place from a normal uterus if ovulation is occurring regularly. The corollary to this is that some pathologic state must account for the abnormal bleeding. There is a growing recognition that this combination of abnormal but characteristically regular bleeding with secretory endometrium actually represents a clinical entity different from that of true functional bleeding, and it has had the somewhat unfortunate term "irregular shedding of the endometrium" attached to it. There is a vague implication that this is due to a functional disturbance of the corpus luteum, but more than enough histologic evidence has been offered to establish

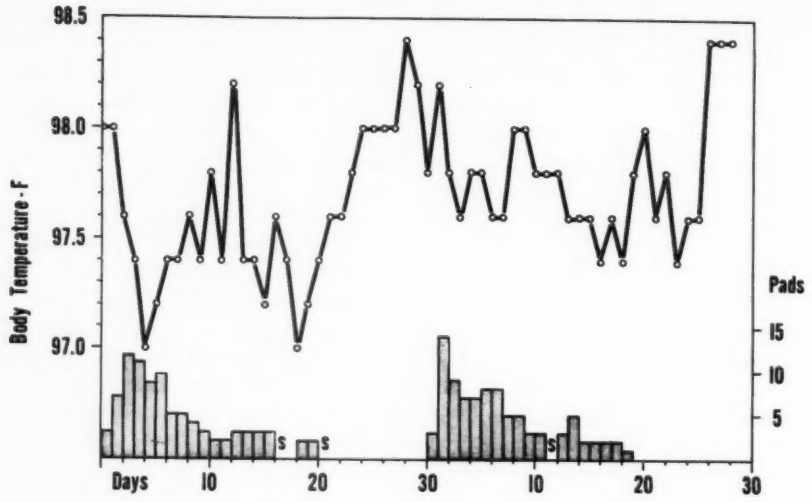


FIGURE 3. Body temperature and bleeding record of a patient with uterine fibroids. This 30 year old woman had always thought of her periods as being irregular, but it was not until she kept a daily record of them that their regularity became apparent. The body temperature record shows an obvious biphasic pattern, and enables one to see that menstrual flow started at the expected normal time, but was prolonged into the preovulatory portion of the next cycle. This evidence was enough to justify an examination under anesthesia, at which time a definitely irregular and somewhat enlarged uterus was easily palpated. Laparotomy showed the presence of numerous fibroids, including one large submucous one. Following the operation, she had two normal periods before she conceived. She was delivered of a normal full-term infant by cesarean section about one year after the operation.

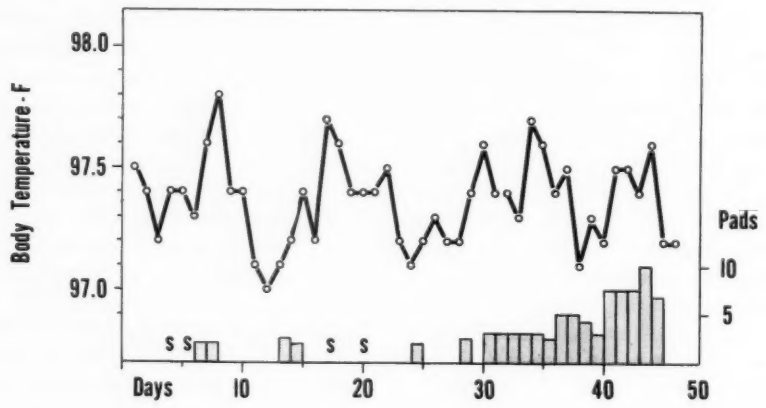


FIGURE 4. Body temperature and bleeding record of a patient with true anovulatory irregular bleeding. Only 46 days of this 28 year old woman's menstrual history are shown here, but they are typical of most of it. Neither the bleeding nor the body temperature record shows a consistent pattern. Numerous endometrial biopsies and several curettages have yielded only proliferative or hyperplastic endometrium. She is still under treatment, and there has been some control of her bleeding with progesterone administered once in four weeks (50 mg.), but she has not yet ovulated spontaneously.

an organic pathologic basis for it, while no one, to my knowledge, has presented satisfactory direct evidence that the life of the corpus luteum, or the secretion of progesterone is any longer in such patients than it is in normal women. But even if we disregard these facts, and grant the possibility that its cause may eventually prove to be functional, it will not alter the thesis of this paper, which is, essentially, that the value of a proper diagnosis is in the opportunity it gives one to institute proper therapy. If the cause of irregular shedding does prove to be functional, it will have to be one associated with ovulation and will, therefore, not be amenable to the same form of treatment that serves to correct anovulatory irregular bleeding.

Conclusions

The physician faced with a patient complaining of abnormal bleeding must first rule out cancer as its cause. When he has done this he must ask himself, "Is my patient ovulating?" As long as her bleeding is not enough to put her in danger (in which case he would have done a dilatation and curettage anyhow) patience is the best course to follow, together with a careful explanation of the importance of a daily recording of both the amount of bleeding and body temperatures. If the latter are taken at the same time each day, read when the patient has enough time to be certain of her accuracy, and recorded in table rather than graph form to reduce the possibilities of error, ovulation will be reflected in a biphasic curve and anovulation in a random distribution of body temperatures. A pattern of bleeding which may not be obvious by itself may suddenly emerge clearly when the bleeding and body temperature records are graphed simultaneously (figure 3); no such pattern will emerge in the true anovulatory bleeder (figure 4).

This approach will yield greater returns in the long run than to conclude hastily that the problem is one of functional bleeding and to immediately institute cyclic hormonal therapy.

The dilatation and curettage which should initiate the diagnostic approach in all patients with abnormal bleeding will of course also help to diagnose ovulation. The endometrial biopsy can also yield enough tissue to show the presence of proliferative, hyperplastic or secretory endometrium and should be used as an adjunct to, but not a replacement of, the body temperature curve.

There is thus nothing fancy about making a proper diagnosis of anovulatory bleeding, just as there is no real problem in diagnosing fibroids as the cause of abnormal bleeding in a patient with a thoroughly relaxed abdomen and a 200 gm. irregular uterus. My plea is only a common sense one: that ovulation is easy to diagnose, that it does not cause functional bleeding, and that abnormal bleeding in the presence of ovulation must be considered as being due to organic disease until all available means to demonstrate it have been exhausted. There will be very few, if any, remaining causes if this principle is adhered to.

POSTGRADUATE MEDICAL DEBATE

Personality Studies

Clinical Evaluation

LEO KANNER*

The Johns Hopkins University School of Medicine, Baltimore

Psychometric Evaluation

STARKE R. HATHAWAY†

University of Minnesota Medical School, Minneapolis

Statement by Dr. Kanner:

THROUGHOUT the ages, medical progress has been enhanced by the introduction of methods aiming at concrete, objectively demonstrable, measurable observations. More especially, the phenomenal advances in the natural sciences during the past century have enabled the clinician to extend his sense of perception and to penetrate areas formerly shrouded in darkness. The resulting new methods have become indispensable aids to diagnosis; however, no instrument or procedure alone has ever been credited with the effective displacement of clinical judgment. One might say that the clinician is the central agent who evaluates a patient's condition on the basis of anamnesis, symptoms and over-all examination plus, to be sure, the data from specific laboratory tests. It is for this reason, for instance, that electrocardiography has not replaced clinical cardiology, and that a series of chemical tests or roentgenograms has not dislodged the need for internal medicine.

LEO KANNER

Until the turn of the century, the study of personality had been limited by the absence of reliable criteria for assessing individual peculiarities. In essence, man had been dealt with as if he were a member of a homogeneous category. However excellent, treatises on mind, morals, reasoning and emotion discussed these issues in general terms as attributes of the species. Beyond clumsy attempts at typology, differences in people were not considered in anything more than epithetic condensations derived from a mixture of empiricism and intuition.

Psychology came to the rescue. Bidding farewell to armchair cogitations and elegant

*Professor of Child Psychiatry, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

†Director, Division of Clinical Psychology, University of Minnesota Medical School, Minneapolis, Minnesota.

discourses, psychologists came into actual contact with the people whom their meditating and writing predecessors had viewed from afar. Experiments and measurements came into their own. To Alfred Binet goes the credit for starting an era of subjecting numbers of persons to certain tasks, establishing averages or majority responses, noting the deviations, and arriving at a numerically ascertainable judgment of a person by comparing his responses with those of others. The avidity with which this innovation was seized on can be realized from its rapid spread, the multitude of imitations and modifications, and, above all, from the peculiar semantic fallacy indulged in by those who used it. The tests were dubbed mental tests, and the procedure was called psychometry; thus, at least terminologically, the fiction was created that by probing a limited area of functioning the measurement was applied to the mind or psyche.

A departure from such naïve generalizations derived from fractional performances led to more ambitious enterprises intended to devise measurable and (on the strength of the measurements) standardized ways of assessing personality *in toto*. It was hoped that trait inventories, projective technics and multiphasic tests would produce a reasonably accurate portrait which, moreover, could be fitted into a carefully calculated diagnostic frame. Thus, because of the untiring and often ingenious endeavors in the direction of psychologic anthropometry, we are at present confronted with what amounts almost to an avalanche of intelligence, aptitude, achievement, character and personality tests, and painstaking attempts at validations and correlations. The "Fourth Mental Measurement Book," edited by Buros, listed 830 tests in 1953.

No unbiased clinician will deny the enormous contributions which psychologic measurements have made to the recorded recognition of the heterogeneity of man. He will not fail to avail himself gratefully of certain insights obtained through the tests. However, he also knows that even if all the pertinent tests were applied to any one of his patients the results would not add up to an all-embracing composite picture that could serve as both a step toward true understanding and a workable introduction to therapy. Peculiar though this may sound, while the tests reveal the personality of a person, the clinician is interested in both the person and his personality. Psychologic measurements are set up to find a comprehensive answer to the question: What methods can we devise to enable us to *tell* as much as possible about an individual's personality? Clinical evaluation is guided by the question: What must we know about a patient in order to be able to *do* something on his behalf?

The clinician is motivated primarily by the desire to help. His activities are directed toward this goal. His choice and use of diagnostic tools are a means to an end. To achieve his goal, he needs a perspective which is based on an integrated appraisal of the kind of a person his patient is, of what has made him what he is, and, significantly, of what has happened and is happening *to* him as well as *within* him. Even the most broadly conceived test results represent time-limited and action-limited centrifugal responses to structured situations which at best touch tangentially on the important centripetal forces that have imparted their specific meaning to the patient. Such forces must be given due consideration in the therapeutic strategy. This consideration goes far beyond the substantival and adjectival snapshot summaries of test analyses, particularly when such summaries are couched in terms borrowed from psychiatric nomenclature, which is not yet fully clarified, or from insufficiently validated psychoanalytic concepts.

The clinician's task and responsibilities are therefore broader than those of the tester. The indisputable help which he receives from psychologic measurements is only a part of an over-all effort to become acquainted with the patient, an effort which must include consideration of the patient's life story and situation, his physical condition, his relationships with his fellow men, and the social and cultural impacts by which he is influenced. The clinician's appreciation of the measurements is attested by the fact that every psychiatric unit has at least one psychologist on its staff who is regarded as a highly valued contributor. But,

keenly aware of his medical obligations, the clinician insists on his right and duty to make diagnostic and prognostic evaluations and to guard against unwarranted encroachments by a few overzealous people who would make such judgments peremptorily on the basis of psychologic measurements alone.

Statement by Dr. Hathaway:

STARKE R. HATHAWAY

SOME definitions may be appropriate to outline the area of debate and to make the arguments more succinct. It is difficult to define personality, but, as used in the following context, the term will be restricted to those aspects of psychologic individuality that are commonly of concern to the clinician. The decisions connoted will be of the sort characterized by words like depressed, elated, hopeless, suicidal, grandiose, labile in emotion, and many other such terms pertinent to evaluation of the psychologic state of a patient. Treatment, referral, management, diagnosis and prognosis decisions rest on such evaluations. In general, these aspects of personality treat with mood and affect but in a modern sense also relate to the patient's motivations, values and wishes. In understanding almost any patient, some estimations of these aspects of the psyche must be made. For the present argument we are considering that the estimations can be attained in one of two contrasting methods of procedure: clinically or psychometrically.

Clinical evaluations are products of the examiner's deliberation about the data from his observation of the patient. Such data are verbal reports, physiologic tests, or observed items such as blushing or tremor. Psychologic test data may also be used, but there is no close adherence to standard procedures. The clinician feels free to use only part of a test, to vary the directions, or to reinterpret the test scores in individual ways. The following are common elements in clinical evaluation: (1) The data may be modified by the examiner. The examiner depends on his judgment to determine if the patient is depressed, lacks appropriate affect, and the like. Even if part of the data used are test data, these are unapologetically combined with nontest data and the examiner feels free to modify the standards according to his judgment. (2) The material used in clinical judgment is not easily put into mensural form. The judgments imply amount but are rarely stated as numerical quantities. One says a patient is "very" depressed but not that he is 10 units depressed. The most frequent form of clinical evaluation is an all-or-nothing statement: "This patient is depressed" or "this patient lacks motivation." When there are elements of quantification implied, we commonly say that a patient is "somewhat" suicidal or that he shows "some" grandiosity. (3) The outcome of clinical judgment is a product of the examiner's synthesis of the data. No one else can produce this outcome by formula. (4) The evaluations are related to the past experiences and to the remembered education of the clinician. The clinical evaluation is of the form, "Cases like this one, in my experience, . . ." or "These symptoms are like a case described by. . . ."

By contrast, psychometric evaluation proceeds by the use of psychologic tests in addition to other tests and observations. These psychologic tests can be on intelligence, personality, aptitude, interest or knowledge. The following are common elements in these tests and in psychometric evaluations: (1) The data, often called items, on which psychologic tests are based are taken directly from the patient without modification by the observer. The patient marks an answer sheet, sorts a card into a "true" pile, or makes an oral response that, with little interpretation by the examiner, permits the examiner to do one of these. (2) The responses are directly in mensural form or they can be immediately given numerical values. (3) The results of the test are either item responses or combinations of these. (4) The evaluations are related to the validation of the test. This means that the evaluations of the patient are tied to past experience by a clerical process that relates the

patient to the recorded data from past uses of the test. All these common elements decrease the liberty of the examiner; they decrease his use of clinical intuition and experience. They signify a corresponding increase in rigidity of data collection and evaluation.

From measurement, broadly characterized in this case as psychometric data, one gets predominantly quantitative statements: A patient has a certain score on a depression scale; his I.Q. is at a certain value; his interests are more like those of a lawyer than like those of a physician, and so on. These measurement data are understood to have probable error limits which, in the best examples of measurement, are relatively well defined. One says that, in the degree to which he can be thought of as appropriately measured by the given instrument, the subject or patient is properly described by the resultant quantitative index. This index or score is then qualified by the established statistical confidence that the true estimate lies within some designated range. Nothing in the concept of measurement requires that a specific measurement is exact or invariant.

In general, science tends to thrive on mensuration. As a science develops, and the usual examples are in natural science, measurement becomes more and more the chief concern in the application of the science. Warmth and cold were, of course, recognized by primitive man. Physical science made great strides when the change occurred from subjective warmth and cold to the use of a thermometer which would indicate the construct which we signify by the word temperature. The first attempts in using a thermometer produced resistance on the part of people who pointed out that the thermometer indicated sometimes that it was warmer than they experienced it to be, and there were other disagreements between what seemed obvious to direct judgment and what the thermometer indicated. When temperature came to be accepted as more closely related to what the thermometer indicates than to what the experiencing observer felt, then science progressed. Today this progress in temperature estimation is so well established that we are hardly able to appreciate how resistant people once were to giving up the right to judge temperature individually.

The essence of this argument is that if we are debating the appraisal of personality by measurement in a context contrasting this with clinical study, we must assign the higher value to measurement because measurement and science are inseparable. Although it is true that some cultures have chosen otherwise, Western culture has accepted science as a value by its adoption of science as a core characteristic of progress. Resistance to extending mensuration into personality evaluation has always been apparent. A kind of dual position may be taken by those who resist in which they assert that such physical items as temperature are appropriately reduced to measurement, but that the psychologic complexities of human thought, emotion and desire will always defy measurement; and the bridge from prescientific to scientific method cannot be crossed for such variables. Looked at in this way, we would deny to human psychology the ultimate successful application of metric science as we know it today.

Whatever the strength of this argument may be, psychologic measurement nevertheless is an established fact. We accept the use and value of intelligence tests and of tests of knowledge in the establishment of grades in courses; in other areas, tests measuring psychologic variables are displacing clinical evaluation. It would seem that we have already made the value choice between measurement and clinical estimation as these would apply to large areas of psychologic life.

We still must consider the argument as it might apply to an individual patient with his individual complaints. Even if one accepts the argument that the psychometric method is superior for group surveys, application to the single case may be objected to as inappropriate. It is true that one patient has peculiarities not predicted from class data, but individual diagnosis can only derive from recognition of the class. No two cases of mumps present identical symptom patterns, but the most significant step in every case is the assignment of the class diagnosis. The extreme of the clinical method in psychologic disorders is

often stated as though no class exists; no diagnosis is possible. Admitting the weaknesses of available psychologic tests and diagnostic systems, it is still hard to see how one can argue that using no system (describing each case differently) or using a system private to the clinician is any better. The very meanings of the term individuality are against science and accumulation of principles for practice. These virtues come from measurement, however inaccurate it may be.

In clinical evaluation the information from the patient is always intermingled with the psychologic contributions of the examiner. Clinical evaluation of personality signifies an examiner making statements about a patient from the examiner's point of view and experience. Inevitably, the result is not reproducible by another examiner. Another examiner will have had different experience and will evaluate differently. In contrast, psychometric data come only from the patient. The patient answers problems correctly or says "True" or "False" to items concerning his personality. These data are produced in part, of course, by the interaction of the experimenter and subject, so that the responses given to a psychiatrist may be different from those given to a prospective employer; nevertheless, the results of a test are much in contrast with clinical judgment in reproducibility and in complexity, since only one person instead of two must be understood in the evaluation of the data by a third person. Old-time physicians could make clinical diagnoses of patients and identify with considerable accuracy the various common diseases, but with the progression of science this skill has languished in favor of laboratory data. Findings from the blood picture, the urinalysis or the radiogram more accurately, with greater reproducibility and within established probable errors, focus the diagnostic conclusions. The change here is parallel to the supplementation of clinical evaluation by psychometric study of personality. A student studying internal medicine today may produce a diagnosis chiefly from a series of laboratory studies which can be evaluated by the instructor, and errors of omission or particular emphasis can be indicated to the student for his training. This is a great advance over the older practice in which the apprentice developed clinical skill by working with a particular instructor, discovering what evaluations were made of patients by the preceptor, and learning to make similar diagnoses from his own perceptions of the patients. The data used by the instructor and the student were inevitably different, since they observed the patient differently and had different approaches to the evaluation. Instruction could not develop reproducible decisions, since the data and syntheses from which the conclusions were drawn could not, as with modern laboratory data, be clearly and in similar fashion obtained and combined by teacher and pupil.

Another way of saying all this is to state that psychometric and other laboratory test approaches depict patient and test data. With clinical evaluation a third person sees the patient, the data and the examiner. In the psychometric approach, a third person could look at the patient and the test data and have what is needed to decide on the value of the conclusions drawn by the examiner. In the clinical approach, the third person must look at the patient and at the qualities and standing of the examiner in order to evaluate the weight to be placed on the examiner's conclusions.

Only with the use of measuring instruments can we compare one patient with others, or groups of patients in one setting with groups in some distant setting, and build up an objective body of professional knowledge. Research and measurement are closely related; the evaluative descriptions of the clinician cannot be conveyed to anyone else, except perhaps to his close associates or to students who have been indoctrinated by him. Clinical evaluations thus have a sort of mortality, tending to be lost when the clinician disappears from the scene; in contrast, psychometric test data and evaluations may survive and be sent all around the country. They have a relative immortality. In the foregoing argument we are seeing the issues from the standpoint of putting the psychometric data and evaluations in the same position as we put the clinical examiner. When using psychometric evaluations,

the tests and their scores provide the data; when using a clinician, he provides the data and is in the position of a test.

Finally, the psychometric method permits accumulation of rarely occurring patterns of personality which, as test data, can be preserved for years so that a new case can be compared, even in novel aspects which might not have been thought of originally. Obviously, purely clinical accumulation of such a body of data is impossible except within the lifetime and personal influence of each clinician. With the personality test as an example, however, we may go back to the old test data and identify constellations of item responses that were made years ago, discovering in these an objective and direct relationship to some newly found constellation belonging to a similar modern case.

These arguments in favor of the psychometric method share many shortcomings with the arguments for the clinical method. Making a case either way chiefly emphasizes the great need for research and inspiration in psychologic medicine. It is obvious to most of us that behavioral science is lagging dangerously behind physical science. There has not been a scientific breakthrough in psychologic medicine remotely comparable to the development of antibiotic chemistry or of new methods in clinical surgery. Our unifying conclusion is that we must gather momentum for a crash program in medical psychology in particular and in the behavioral sciences in general.

Comment by Dr. Kanner:

The case for clinical evaluation was made with full acknowledgment of the value of psychologic measurements. The parallel drawn by Dr. Hathaway between psychometry and the laboratory data employed in internal medicine invites the conclusion that tests of any kind are useful in the clinician's search for diagnosis and hence as a step toward therapy. With this there can be no disagreement. The "resistance to extending mensuration into personality evaluation" of which Dr. Hathaway speaks simply does not exist; but there is strong and justified resistance to an assignment of hierarchic status contained in the categorical assertion that tests are of "higher" rank than clinical perspective.

The clinician cannot and must not assume the role of a detached, impersonal computer of assorted test results. If his judgment admittedly is not infallible, neither is psychometry infallible. But the clinician has a task before him which transcends anyone's obsessive desire for theoretically unshakable accuracy—with the humility which springs from awareness of the imperfection of human endeavor he sees his job as an all-out effort to alleviate suffering and, though grateful for any practical help which comes to him from psychometric studies, is not too perturbed when a numerical tag is not affixed to the nature and extent of the suffering. In this sense, Dr. Hathaway's characterization of psychometry as "the supplementation of clinical evaluation" is a fitting basis for noncontroversial collaboration.

Comment by Dr. Hathaway:

Dr. Kanner's statement seems to be pervaded by a somewhat old-fashioned contrast, clinician with psychometrist. This is like contrasting the internist with the laboratory technician. From such a position, the argument is unfairly set up and unanswerably in favor of the clinician.

The interesting argument more properly centers about two responsible clinicians—the one using clinical evaluation is free to modify test data and to get along without them as the situation indicates, and the other largely relies on psychometric data collected by a psychometrist or collected by the clinician himself using standard conditions.

Dr. Kanner points out, and I agree with him, that there has been a tendency to identify psychometric results with the construct "mind" or "psyche." It is certainly true that the mind or psyche transcends any one measure or any large pattern of measurement. It is unthinkable that any clinician would narrow his thinking to an "adjectival snapshot" in favor of a set of measurements, allowing these to stand entirely by themselves. Synthesis is necessary in every case and the argument chiefly concerns the degree to which the clinician's judgment

is used in the synthesization and around the level at which his judgment enters. The clinical clinician enters synthesis early and modifies radically; the psychometric clinician enters with reluctance and modifies standard findings as little as possible.

It is difficult to understand the differentiation of a "person" and his "personality." Dr. Kanner grants that ". . . tests reveal the personality of a person . . ." (about which point I would be doubtful) but then attributes to clinical evaluation the question, "What must we know about a patient in order to be able to *do* something on his behalf?" It is to such questions that I would particularly apply the argument that psychometric evaluation is the proper approach for the clinician.

Finally, I cannot differentiate clinicians in psychometric versus clinical evaluation on the basis of sampling. Both approaches seem "time-limited" to me, but the psychometric approach is less time-limited than is the clinical approach. The clinical approach is too responsive to diagnostic fashions. The patient must be protected from the uncontrolled aspects of the clinical method. Psychometric evaluation imposes stability; it could be argued sometimes that it imposes too much stability, but the sampling argument operates in favor of measurement.

1958

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 10-13 Municipal Auditorium Cleveland, Ohio

Drug Therapy of Hypertension in Old Age

ROBERT W. WILKINS, M.D.

Professor of Medicine, Boston University School of Medicine, Boston

In determining the need for drug therapy of hypertension in old age, importance is attached only to elevations of diastolic, not of systolic, pressure. Drug therapy should be conservative and designed to moderate the diastolic pressure gradually, not to normalize it suddenly. *Rauwolfia, Veratrum,* occasionally APRESOLINE®, and chlorothiazide may be used with care, either in combination or alone, as indicated by the patient's response. Dietotherapy designed especially to reduce weight and, if possible, to lessen the danger of atherosclerosis is also employed.

Clinical Physiology of the Pituitary Gland

LAURANCE W. KINSELL*

Highland-Alameda County Hospital, Oakland, California

LAURANCE W. KINSELL

THE pituitary gland is a small organ lying in the sella turcica at the base of the skull. It is divided into two parts anatomically and developmentally. The anterior portion is derived from Rathke's pouch; the posterior lobe is derived from the infundibular process of the brain.

The known hormones of the anterior lobe are shown diagrammatically in figure 1. In addition, the diabetogenic, erythropoietic and fat-mobilizing factors will be considered. If one is to understand the relationship of these various hormones to clinical physiology in man, it may be well to be aware of the clinical entities which result when too little or too much of the hormones is produced (table 1), and to consider each hormone individually.

*Director, Institute for Metabolic Research, Highland-Alameda County Hospital, Oakland, California.

Hormones of the Anterior Lobe Which Produce Their Effects Directly

Pituitary growth hormone (somatotropin)—As its name would imply, this hormone regulates growth. It is probably secreted by the eosinophilic cells. Excessive production of this hormone results in gigantism or acromegaly (figure 2). Inadequate production or lack of production results in retardation of growth or dwarfism (figure 3).

Gigantism and acromegaly—For clinical purposes, one may consider growth under two headings: (1) growth of soft tissues, and (2) growth of the skeleton. As far as is known, the growth hormone affects all tissues, including the skeleton. There is considerable evidence which suggests that it may have a greater effect on connective tissue, including bone, than on muscle.

Growth of the skeleton has two major phases: (1) growth per se, and (2) maturation. Growth of the cartilaginous plate known as the epiphysis results in lengthening of bones. So long as this plate remains uncalcified, linear

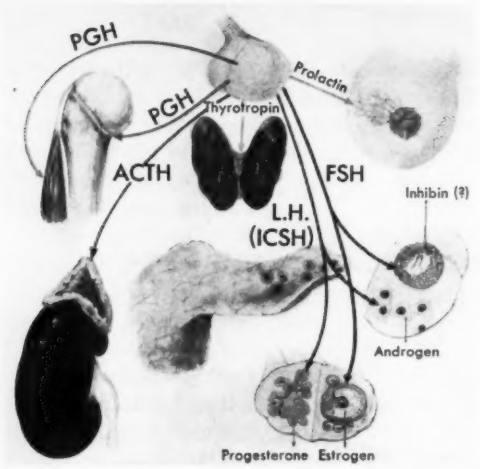


FIGURE 1. Known anterior pituitary hormones. Growth hormone and prolactin act directly on peripheral cells. The other anterior pituitary hormones act indirectly through other endocrine glands.

growth may continue indefinitely. The growth-promoting effect of the pituitary growth hormone differs from the growth-promoting effect which anabolic steroid hormones produce (see following discussion). The pituitary growth hormone stimulates growth to a relatively greater degree than it does maturation. As a result, epiphysial closure does not occur.

Gigantism results from a tumor or hyperplasia of the eosinophilic cells of the anterior lobe. Its onset occurs *before* closure of the epiphyses of the long bones. Patients with this disease have grown to be 9 ft. tall. Probably because of the greater stimulation of connective tissue growth than of muscle growth, the patients are strong in the early phase of the disease, but tend to become weak as the disease progresses, i.e., as skeletal development outstrips muscular development. In the early stages of the disease, the patients may be unusually strong, and endurance and libido may be increased.

Acromegaly also results from a tumor or hyperplasia of the eosinophilic cells of the anterior lobe, but its onset occurs *after* the epiphyses of the long bones have closed. As a result of stimulation of periosteal bone growth, most bones become thickened progressively. The characteristic acromegalic appearance is shown in figure 2.

Ideally, the clinical diagnosis of any endocrine disease is made by measuring the amount of the responsible hormone in the blood and urine and by comparing this with the amount found in the blood and urine of normal persons. As yet, no such method is available for the diagnosis of diseases due to the pituitary growth hormone. Consequently, the *diagnosis* of gigantism and acromegaly is made chiefly on the basis of the following findings:

1. A history of increased total growth, or of increased shoe size or glove size in cases of acromegaly.

2. Roentgenographic evidence of enlargement of the sella turcica. In an occasional case, such enlargement is not present.

3. Clinical and roentgenologic evidence of characteristic changes in the bones. These changes include broadening and tufting of the

TABLE 1

SYNDROMES RESULTING FROM ANTERIOR PITUITARY DISEASE

HORMONE	TOO MUCH	TOO LITTLE
Growth	Acromegaly and gigantism	Dwarfism
Prolactin	Galactorrhea	No lactation
Thyrotropin	Hyperthyroidism	Hypothyroidism and myxedema
Adrenocorticotropins	Cushing's disease and adrenogenital syndrome	Addison's disease; impaired resistance to many diseases
Follicle-stimulating	Associated with menopause	Hypogonadism
Luteinizing	Hyperthecosis (?)	Hypogonadism

phalanges, widening of the vertebral bodies, increased spacing of the teeth as a result of the growth of the jaws, prominence of the supra-orbital ridges, and thickening of the tables of the skull. The widening of the vertebral bodies frequently is associated with marked lordosis, or it may be partially due to the greater growth of bone than of the ligaments.

4. An increase in the concentration of serum inorganic phosphorus.

The two major *complications* are: (1) interference with other functions of the pituitary as the result of encroachment by an eosinophil adenoma and (2) encroachment on the optic nerve by an expanding tumor or cystic degeneration of a tumor, with resultant production of bitemporal hemianopsia, which may progress to complete blindness. The interference with other functions of the pituitary may be manifested by amenorrhea in the female, by impotency, little or no sperm, small testes and prostate in the male, by disturbances in thyroid function usually associated with a colloid type of goiter, and by lactation in both sexes, probably the result of the production of prolactin by the eosinophil cells.

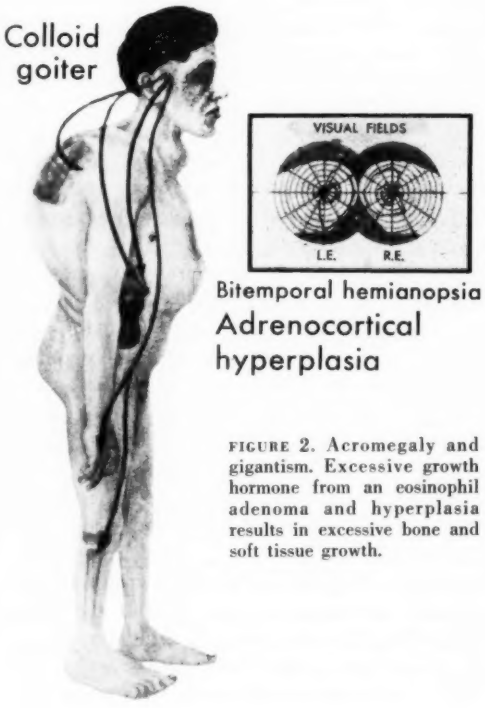


FIGURE 2. Acromegaly and gigantism. Excessive growth hormone from an eosinophil adenoma and hyperplasia results in excessive bone and soft tissue growth.

Hormonal therapy, irradiation and operation are the three types of *treatment* used at the present time. There is less than full agreement among different authors as to the best type of treatment. At the Institute for Metabolic Research of the Highland-Alameda County Hospital, we prefer to use *hormonal therapy*. In cases in which the patients are males, testosterone is administered intensively. A very satisfactory preparation for this purpose is testosterone cyclopentylpropionate. A dose of 200 mg. of this preparation is administered twice a week, and its administration is continued until the concentration of the serum inorganic phosphorus falls to 3.5 mg. per 100 ml. The dose is then reduced to that amount which will maintain the concentration of the serum inorganic phosphorus below 4 mg. per 100 ml.

In cases of acromegaly in which the patients are females, estrogen, usually ethinyl estradiol, is administered daily in doses of 0.05 to 0.5 mg. As in cases in which the patients are males, the dose of the hormone is regulated to achieve and maintain the concentration of serum inorganic phosphorus below 4 mg. per 100 ml. In cases in which these doses of estrogen are administered, it will be necessary to discontinue its administration for five days of each calendar month in order to permit withdrawal bleeding. If there is any tendency toward intermenstrual spotting or excessive bleeding, progesterone must be administered during the five days of withdrawal of estrogen (25 mg. daily orally or 10 mg. daily by intramuscular injection).

The rationale of this therapy is as follows: In essentially all cases of acromegaly except those in which the patients are normally menstruating women, the concentration of serum inorganic phosphorus is increased. This statement also applies to prepuberal children. At the time of puberty, with its associated production of androgen or estrogen, the concentration of serum inorganic phosphorus falls to that of normal adult values. It seems, there-

fore, that the concentration of the serum inorganic phosphorus (assuming that there are no other factors, such as advanced renal or parathyroid disease) is an index of the production of the pituitary growth hormone and of its peripheral effects.

The anabolic steroids presumably inhibit the production or effects of the pituitary growth hormone and cause the concentration of the serum inorganic phosphorus to fall to normal adult values. They thus control the progression of the disease, and may produce improvement in the signs and symptoms.

Since the pituitary gland is only mildly sensitive to *radiation*, very intensive dosage must be used in order to affect an eosinophil adenoma. It has been my experience that even this dosage does not control the tumor adequately in most cases. It is for this reason that we use radiation therapy only in cases in which progression of bitemporal hemianopsia indicates that the tumor is encroaching on the optic nerve. Focused ultrahigh-frequency radiation therapy, e.g., the use of the deuteron beam, may be much more effective.

It is the opinion of essentially all authors that *operation* should be done only in cases in which, despite the use of hormonal and radiation therapy, encroachment on the optic nerve progresses or fails to regress. Operation should be performed only by highly skilled neurosurgeons.

Pituitary dwarfism—By definition, pituitary dwarfism (figure 3) is the opposite of pituitary gigantism. It may be due to a congenital abnormality or absence of the pituitary gland, or to destruction of the gland by a tumor or other means. The tumors that are most likely to cause this condition are chromophobe adenomas and craniopharyngiomas, with or without cystic degeneration and calcification.

In cases of congenital pituitary dwarfism, the *diagnosis* is made on the basis of the following clinical features. When a child with this disease is five or six years old, it will be noted that he is somewhat shorter than other children of the same age; when he is nine years old, it will be noted that he is markedly shorter. Evaluation of the "bone age" on the basis of the epiphysial development shows

FIGURE 3. Pituitary dwarfism and hypogonadism. Pituitary dwarfism-hypogonadism may result from pituitary hypoplasia or pituitary destruction. Adrenocortical insufficiency is rarely present in the "idiopathic" variety.

marked retardation. The same statement applies to dentition. When the child is 15 years old, it will become very apparent that his development has lagged far behind that of other children of the same age, and there will not be any evidence of the development of puberty. After he is about 35 years old, premature aging will occur, and, if he lives to be 40 or 50 years old, he will be an old-young, gnome type of person with dry, wrinkled, fawn-colored skin. Very few persons with congenital pituitary dwarfism live to be 50 years old.

In cases in which pituitary dwarfism is due to a tumor, a variety of signs and symptoms referable to local pressure may be present. A complete lack of gonadotropin production, some impairment of the production of thyrotropin and the diabetogenic factor, and slight impairment in the production of corticotropin are present in most cases of congenital pituitary dwarfism.

In the *differential diagnosis*, cretinism and juvenile myxedema, Tom Thumb dwarfism, achondroplasia and related conditions, gonadal dysgenesis, and short stature associated with pseudohypoparathyroidism must be con-

sidered. In addition to the characteristic mental and physical findings in cases of *cretinism and juvenile myxedema,* the impressive response to adequate thyroid medication is a very important differential factor if such medication is instituted in time. In cases of *achondroplasia and related conditions,* the size of the trunk is normal, the extremities are short, the head is relatively large, and the findings at the ends of the long bones are characteristic. The cause of dwarfism in cases of *gonadal dysgenesis* is unclear. It is associated with many other congenital anomalies. The bone age tends to be normal, and epiphysial closure usually occurs before the age of 20 years. Very poor growth response occurs when steroid anabolic hormones are administered. The diagnosis of *short stature associated with pseudohypoparathyroidism* is made on the basis of the presence of hypocalcemia and the other characteristic findings.

Among the *complications* of pituitary dwarfism are neurologic symptoms due to focal pressure by a suprasellar or intrasellar tumor. In cases in which a serious lack of production of ACTH is associated with inadequate production of the pituitary growth hormone, increased susceptibility to infection and to stress in general may be present. This is more likely to be present in the acquired than in the congenital form of the disease.

Despite the fact that pituitary extracts (mostly bovine) which will produce growth in experimental animals have been available for more than 30 years, there is still no available growth hormone which will produce satisfactory results in human beings. Recent work in which growth hormone derived from the pituitary glands of monkeys produced growth in these animals (a species also resistant to the bovine growth hormone) has indicated that a high degree of species specificity exists in the case of the growth hormone. It is to be hoped that protein chemists may eventually find means to rearrange some of the amino acid structure of bovine growth hormone so that it will be effective in human beings. For obvious reasons, the supply of growth hormone from the pituitary glands of human beings never will be plentiful. The size of the growth hormone molecule (molecular weight 40,000 to 50,000) makes the possibility of synthesis negligible.

The *treatment* of pituitary dwarfism is limited to the administration of extrapituitary hormones which are lacking. Some growth may be induced by the administration of small doses of anabolic steroids such as testosterone and related compounds. Because these compounds have a tendency to stimulate epiphysial maturation to a greater degree than epiphysial growth, it is important to use the smallest effective therapeutic dose. Some clinicians believe that these doses should be combined with the largest tolerated doses of desiccated thyroid or a similar preparation in an effort to produce the greatest amount of growth before closure of the epiphyses.

Prolactin—The literature contains reports of cases in which a small tumor of the pituitary has caused an increased production of prolactin, which resulted in constant lactation. A relative or absolute amenorrhea usually is present in such cases, and other endocrine abnormalities also may be present.

Diabetogenic and fat-mobilizing hormones—These two extremely important hormones will be considered only briefly because of the lack of adequate knowledge of the way in which they act, and because of the lack of sufficiently purified materials to permit any precisely controlled studies. The following statements appear to be in accord with the facts.

The diabetogenic factor* has not yet been separated from the growth hormone. Many investigators believe that it is identical with the growth hormone. I believe that it is a separate hormonal entity and that it eventually will be separated from the growth hormone complex. It is probable that the same cell produces both of these hormonal factors. There is reason to believe that the diabetogenic factor may be concerned with energy production for growth purposes. It probably is of major importance in cases of diabetes. It may well be responsible for some types of extreme resistance to insulin. It also may be partially responsible for

*The term diabetogenic factor is misleading. Obviously, the major function of this factor is not to cause diabetes.

"brittle diabetes" in the child and in some adults. It is my opinion that this factor and cortisone and insulin represent the hormonal triad responsible for normal energy metabolism, particularly with respect to the utilization of carbohydrate and fatty acids.

The *fat-mobilizing hormone* has not yet been separated from highly purified adrenocorticotropin. It seems probable that this is a hormonal entity of major importance. Much experimental work remains to be done before the picture can be brought into focus.

Erythropoietic hormone—Some investigators believe that there is a specific pituitary factor which stimulates the bone marrow to produce red cells. In my opinion, the experimental evidence is not sufficient to warrant this conclusion. It is entirely possible that the combined effects of the thyroid hormone and of certain of the adrenocortical hormones are sufficient to account for the effects which have been attributed to the so-called erythropoietic hormone. Further work will help to clarify this problem.

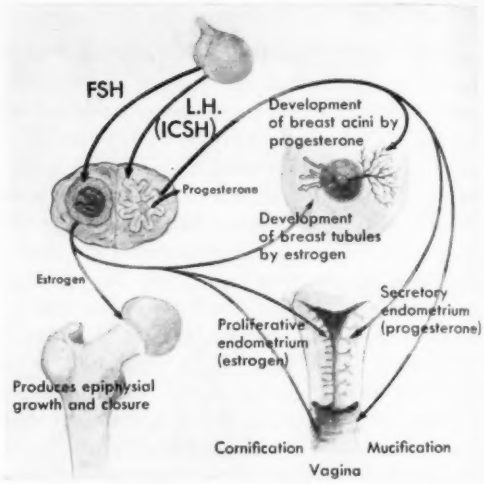


FIGURE 5. Clinical physiology of the female gonads. In response to pituitary gonadotropins, growth and development of the graafian follicle proceed as follows: (1) follicle and ovum maturation, with estrogen production; (2) ovulation, and (3) progesterone secretion by the corpus luteum.

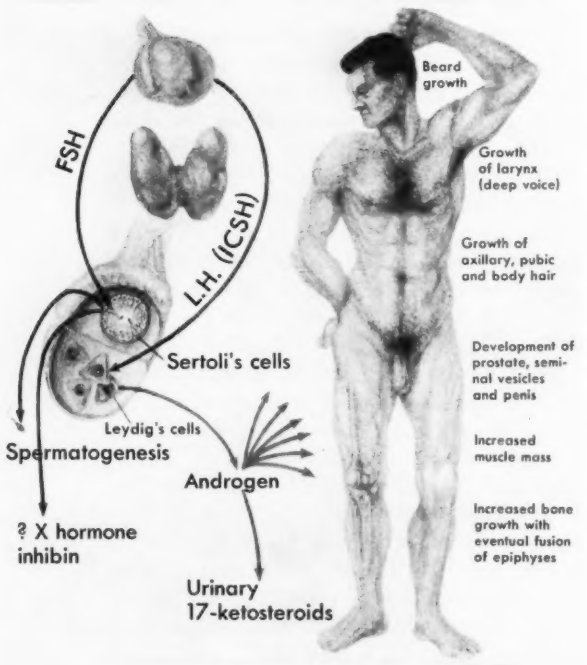


FIGURE 4. Clinical physiology of the male gonads. The Leydig cells of the testis secrete androgen. The Sertoli cells may possibly secrete another hormone (inhibin). Androgen is of importance in (1) the development of the male characteristics, (2) the somatic growth and (3) the spermatogenesis.

Hormones of the Anterior Lobe Which Produce Their Effects by Way of Other Glands of Internal Secretion

Gonadotropins—Before the onset of puberty, the pituitary gland makes little or no gonadotropic material. At the proper time, there is a closure of some circuit which results in the production of gonadotropin. Three gonadotropic principles have been described, namely, *follicle-stimulating hormone* (FSH), *luteotrophin** (luteotrophin may be identical with prolactin), and the *luteinizing hormone* (L. H.). In the female, the follicle-stimulating hormone stimulates the graafian follicle to produce estrogen and mature ova; in the male, it stimulates the seminiferous tubules to produce sperm when androgen is present. In the female, the combined effects of these hormones

*Luteotrophin also is a registered trade name for a proprietary brand of a mixture of gonadotropins.

result in ovulation and in the stimulation of the specific cells of the ruptured follicles to produce progesterone. In the male, the luteinizing hormone, which also is called the *interstitial cell-stimulating hormone* (ICSH), stimulates the interstitial cells of Leydig to produce the male hormone, a substance identical with or similar to testosterone.

All of the primary and secondary sexual characteristics as well as the spurt of pubertal growth are attributable to the effects of the hormones of other endocrine glands which are produced in response to gonadotropin stimulation. These effects are depicted diagrammatically in figures 4 and 5.

At present, there are no known entities which are due to excessive production of gonadotropin. An absence of gonadotropin or an inadequate production of this hormone causes pituitary eunuchoidism in the male and female.

Pituitary eunuchoidism in the male—This condition is depicted diagrammatically in figure 6. Fundamentally, the *diagnosis* is based on a lack of development of primary and secondary sexual characteristics, an absence of urinary gonadotropin, and a normal prepuberal testicular architecture as disclosed by biopsy. This condition may occur alone, in which case growth may continue for many years with resultant eunuchoid habitus, or it may occur in association with some degree of growth impairment as shown in figure 3.

In the *differential diagnosis*, this condition must be distinguished from one of the forms of primary gonadal eunuchoidism. In cases of the latter condition, the production of gonadotropin is increased, and the testes are absent or grossly abnormal.

Because of the lack of dependable or economically feasible preparations of gonadotropin, or both, the best type of *treatment* for this condition is the administration of a long-acting preparation of testosterone. In my experience, one of the best preparations for this purpose has been testosterone cyclopentylpropionate. For maintenance therapy, 100 to 300 mg. of this preparation is administered intramuscularly at intervals of three or four weeks. This hormone will result in normal development of primary and secondary sexual characteristics with the exception of spermatogenesis and gonadal enlargement. Some pituitary eunuchoids will respond to the administration of "chorionic gonadotropin." If one has strong reason to believe that this substance may "trigger" normal production of gonadotropins by the pituitary, it may be worthwhile to administer 2000 to 4000 units two or three times a week for a period of three months. If an excellent response has occurred by the end of this time, therapy should be discontinued to determine whether the progression of puberty will continue without further treatment. In my experience, such progression has not been particularly impressive.

Pituitary eunuchoidism in the female—Pituitary eunuchoidism appears to occur more rarely in the female than it does in the male. As in the male, the *diagnosis* is based on the lack of development of primary and secondary sexual characteristics, with or without abnormality of growth. In the *differential diagnosis*, this condition must be distinguished from primary gonadal eunuchoidism. In cases of pituitary eunuchoidism, there is a lack of uri-

Low hairline
Little or no beard
Small larynx—high voice
Poor musculature
Minimal pubic and axillary hair and genital development
Long arms and legs with delayed closure of epiphysis

FIGURE 6. Pituitary eunuchoidism. Inadequate pituitary gonadotropin production without other pituitary insufficiency occurs fairly commonly in men and occasionally in women.

nary gonadotropin; in cases of primary gonadal eunuchoidism, the amount of gonadotropin in the urine is increased.

In the *treatment* of pituitary eunuchoidism in the female, sufficient estrogen should be administered to produce normal development of the breasts and of other primary and secondary sexual characteristics. In my experience, a most satisfactory preparation has been ethinyl estradiol, which is administered daily in doses of 0.05 mg. After the uterus has developed to a sufficient degree, the administration of this preparation is discontinued during the first five days of each calendar month in order to permit withdrawal bleeding. In some girls, normal growth of axillary and pubic hair will occur during the administration of estrogen. This growth apparently is part of a secondary adrenocortical response to the administration of the estrogen. If this does not occur, or if the libido is subnormal, administration of small amounts of methyltestosterone (rarely more than 5 mg. per day, and sometimes not more than 5 mg. three times a week) usually will be sufficient to produce the desired effect.

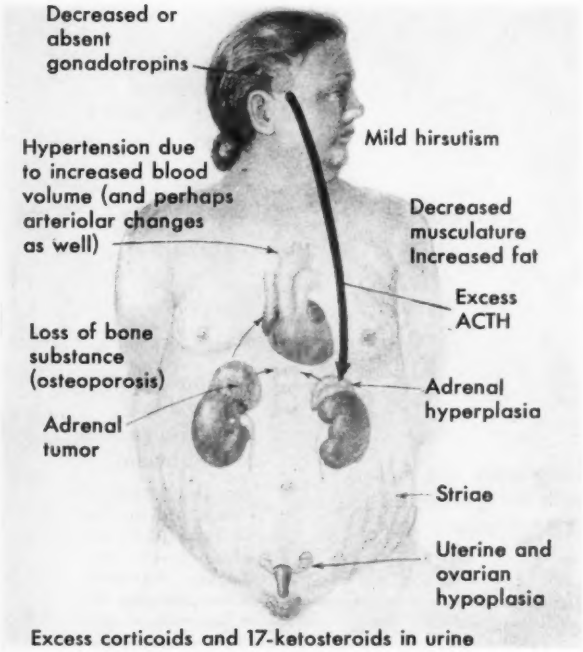


FIGURE 7. Cushing's syndrome, hyperadrenocorticism.

The menopause—In most women, cessation of menstruation occurs between the ages of 42 and 55 years. In association with this, the secretion of estrogen decreases markedly or stops, and large amounts of gonadotropin are found in the urine, i.e., a type of pituitary dysfunction occurs. The ovaries atrophy.

The reasons for the menopause are not entirely clear. It seems most probable that much more than the usually accepted concept of ovarian exhaustion as a result of insufficient primordial follicles is involved. Space will not permit elaboration of this statement.

Administration of physiologic or subphysiologic doses of estrogen controls the signs and symptoms of the menopause. Daily administration of 0.01 to 0.05 mg. of ethinyl estradiol represents satisfactory substitution therapy. Because of the relatively high incidence of osteoporosis among women who have passed the menopause, and because of the lack of untoward effects of properly supervised estrogen therapy, it is my opinion that there are more reasons for using this type of therapy than there are for withholding it.

Adrenocorticotropin (ACTH)—A knowledge of the normal relationship of the pituitary and adrenal glands is necessary for an understanding of the diseases due to adrenocortical dysfunction. The cortical cells of the adrenal gland produce three major types of hormones when normally stimulated by pituitary factors. The production of the *hydrocortisone type of adrenal hormone* and of the *mildly androgenic type of hormone* is essentially entirely under the control of pituitary adrenocorticotropin. The production of *aldosterone*, the salt-and-water-regulating hormone, apparently is partially controlled by adrenocorticotropin, but a certain amount of this adrenal hormone may be produced in the absence of any pituitary activity.

Hyperadrenocorticism (Cushing's syndrome)—This syndrome may be caused by an adrenal tumor or by adrenocortical hyperplasia. The hyperplasia may be due to excessive production of adrenocorticotropin. The salient features of Cushing's syndrome, regard-

less of its cause, are illustrated in figure 7.

The *diagnosis* is based on the following signs and symptoms: progressive rounding of the face, osteoporosis, increasing abdominal striae, hypertension, some hypertrichosis and loss of head hair, progressive muscular weakness, amenorrhea in women or loss of sexual potency in men, ecchymoses and a history of bruising easily, and a significant increase in the excretion of 17-hydroxycorticoids in the urine. The urinary excretion of 17-ketosteroids also may be increased. Contrast roentgenography by means of retroperitoneal injection of oxygen will determine whether or not an adrenal tumor is present. If this diagnostic procedure does not disclose a tumor, the presence of adrenocortical hyperplasia may be presumed.

The only *treatment* for an adrenal tumor is operation. The operation should be performed only in institutions in which an experienced medical-surgical team is available; otherwise, the mortality rate will be unnecessarily high.

If *adrenocortical hyperplasia* is present, two alternatives are open: (1) pituitary irradiation and (2) total adrenalectomy. Many physicians try pituitary irradiation before resorting to total adrenalectomy. If this type of treatment is effective, the response may be dramatic. If an excellent response is not obtained, total adrenalectomy should be performed. Some physicians believe that partial adrenalectomy should be performed rather than total adrenalectomy. In my experience, partial adrenalectomy has not been satisfactory, and a second operation usually has been necessary to remove the remaining portion of the adrenal gland. The preoperative and postoperative treatment of patients with Cushing's syndrome is extremely delicate, and it should be carried out only by physicians who are experienced in the treatment of this syndrome.

Virilizing hyperplasia of the adrenal gland (figure 8)—In cases of this disease, the sequence of events appears to be as follows: (1) abnormal enzymatic structure of the adrenal cortex; (2) consequent production of abnormal virilizing (sometimes "salt-losing") adrenal steroids which do not inhibit the production of ACTH and do not have an adequate hydrocortisone effect; (3) resultant excessive production of ACTH, and consequently a further increase in the production of a more or less androgenic steroid; (4) progressive virilization as a result of this sequence of events, and (5) marked acceleration of growth and of skeletal maturation. A child of six years may have a "bone age" of a child of 14 years or more. As previously noted, the steroid which is produced may not have any sodium-retaining properties.

In the *differential diagnosis,* virilizing hyperplasia should be distinguished from an adrenal tumor. The excretion of 17-ketosteroids usually is increased in cases of adrenal tumor as well as in cases of adrenocortical hyperplasia, but contrast roentgenography of the adrenal gland should disclose a tumor, if one is present. If the diagnosis is still in doubt after this diagnostic procedure has been used, cortisone acetate should be administered intramuscularly, once a day, in doses of 25 mg.

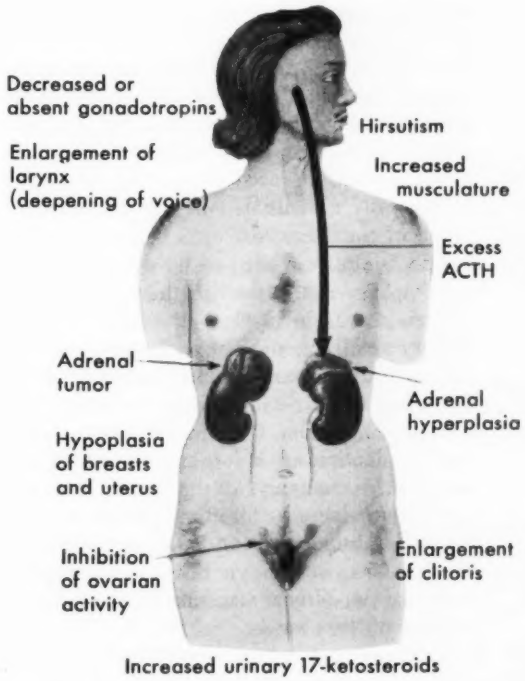


FIGURE 8. Adrenogenital syndrome, hyperadrenocorticism.

If the virilism is due to adrenocortical hyperplasia, the administration of this drug will inhibit the production of ACTH and thus cause a rapid decrease in the urinary excretion of 17-ketosteroids. If this occurs, the permanent treatment consists of the intramuscular administration of cortisone acetate in doses sufficient to maintain the 24 hour excretion of 17-ketosteroids between 5 and 10 mg. in the case of an adult and between 1 and 3 mg. in the case of a child. Usually, not more than 25 mg. of this preparation will have to be administered four to six times a week. This drug also may be administered orally, but this method of administration usually is less satisfactory than intramuscular administration. The administration of cortisone acetate usually results in improvement in the signs of virilism. The time at which the onset of normal puberty will begin depends on the "bone age" at the time the administration of cortisone acetate is started.

Hyperaldosteronism possibly secondary to pituitary dysfunction—This syndrome will be discussed more fully in the paper* on the adrenal gland. In my experience, almost all of the patients with this syndrome have been females whose chief complaint was an excessive accumulation of fluid. Without exception, these women were emotionally unstable, and usually had been so for many years. Such instability is markedly accentuated in the premenstrual phase of the menstrual cycle. This syndrome usually is not associated with hypertension.

Complete restriction of the ingestion of sodium results in marked diuresis. Inclusion of very small amounts of sodium in the diet results in a prompt reaccumulation of the fluid. Thus far, the experimental and clinical findings are compatible with the concept of excessive production of aldosterone or a similar material, presumably as the result of excessive hypothalamic or pituitary activity or both. An exploratory operation has been performed in a few cases of this syndrome, and an abnormality of the adrenal structure has been found in some of these cases.

A second and better-defined type of hyperaldosteronism is associated with hypertension, an increased concentration of serum sodium, and a decreased concentration of serum potassium. Some patients with this type of the syndrome have an adrenal tumor which presumably secretes aldosterone or a similar material. In cases of hyperaldosteronism in which severe progressive hypertension responds well to total adrenalectomy, the syndrome may conceivably be secondary to pituitary dysfunction.

These two types of hyperaldosteronism have been mentioned only for the sake of completeness. If the presence of either of these types of the syndrome is suspected, the patient should be referred to a medical center where appropriate investigation can be carried out.

Pituitary hypoadrenocorticism—This condition rarely exists as an individual entity. It should be treated in the same manner as panhypopituitarism.

Thyrotropin—As shown in figure 1 and table 1, the thyrotropic hormone of the pituitary controls thyroid activity. The clinical findings in cases of hypothyroidism and hyperthyroidism (figure 9) are discussed elsewhere

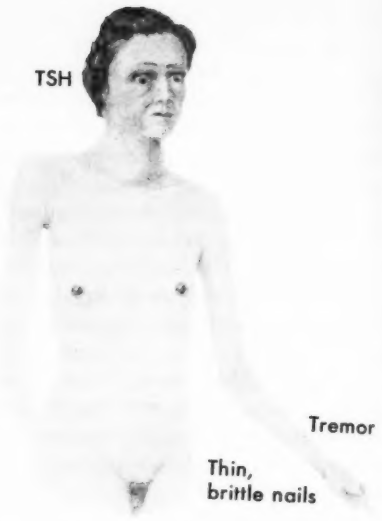


FIGURE 9. Hyperthyroidism, pathologic physiology. Increased production of thyroid hormone results in increased metabolic activity of all cells. The exophthalmos is probably referable to some pituitary hormone effect—perhaps thyrotropin.

*To be published.

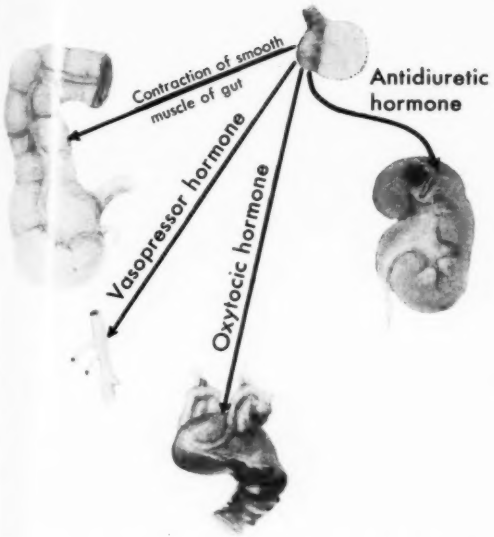


FIGURE 10. Physiologic activity of the posterior pituitary. Destruction of the posterior pituitary results in the syndrome of diabetes insipidus.

in this series of papers. For present purposes, one need only say that the goal of optimal therapy of at least some types of hyperthyroidism is suppression of thyrotropin production. The means of attaining such suppression are not yet available. *Pituitary hypothyroidism* almost never occurs as a separate entity, but is associated with panhypopituitarism.

Highly potent preparations of thyrotropin are available, but they have very little in the way of clinical usefulness. In the treatment of hypothyroidism, one may use thyrotropin if he has reason to suspect that the condition is of pituitary origin. This hormone should be used with some caution, particularly in cases in which the cardiovascular status is at all precarious.

Hormones of the Posterior Lobe

Recent evidence strongly suggests that the posterior lobe of the pituitary *stores* but does not produce the polypeptide hormone complex which is generally known as pituitrin.* This complex, which contains at least two major components, probably is produced in the hypothalamus. It produces the following major effects: (1) stimulation of smooth muscle in the viscera and blood vessels (figure 10), (2) stimulation of the uterine muscle, and (3) stimulation of a portion of the renal tubule to reabsorb water.

Lack of the antidiuretic factor results in *diabetes insipidus*, a disease characterized by an intense thirst, polyuria, and inability to concentrate urine. If the administration of PITRESSIN® tannate (vasopressin tannate) enables the patient to concentrate urine to a specific gravity of 1.018 or higher, it will enable one to distinguish diabetes insipidus from disease of the renal tubules.

Diabetes insipidus may result from a tumor or from unknown causes. The severe form of the disease occurs only if the anterior lobe of the pituitary is intact, but mild forms of the disease may occur in cases of panhypopituitarism. The kidney cannot produce a concentrated urine in cases of either type of the disease. Some authors believe that the inability to concentrate urine is just as important as polyuria in the diagnosis of this disease.

Diabetes insipidus may be controlled satisfactorily by the administration of Pitressin tannate at intervals of two or three days.

Panhypopituitarism (Simmonds' Disease, Sheehan's Syndrome)

As a result of congenital anomalies and tumors situated in the proximity of the sella turcica, there may be a partial or complete absence of the pituitary, or the gland may be destroyed. Severe postpartum hemorrhage also may cause complete destruction of the gland. Very marked hyperplasia of the pituitary occurs during pregnancy. If the postpartum hemorrhage is severe, the blood supply becomes insufficient to maintain the hyperplastic pituitary, and necrosis of the gland occurs. Thrombosis of the nutrient artery may be found.

If the pituitary has been destroyed completely, there will be complete atrophy of the gonads, the adrenal cortex and the thyroid gland, a lack of production of the diabetogenic hormone, and stoppage of growth. In

*Pituitrin also is a registered trade name for a proprietary brand of this hormone complex.

effect, the patient will have progressive myxedema, eunuchoidism and Addison's disease.

In the *differential diagnosis*, panhypopituitarism must be distinguished from anorexia nervosa. In cases of anorexia nervosa, there is no tendency for an addisonian crisis to occur when the patient is subjected to stress. The growth of axillary and pubic hair may be normal or increased, whereas there is an inability of axillary and pubic hair to grow in cases of panhypopituitarism. A characteristic fawn-colored pigmentation occurs in cases of panhypopituitarism.

In cases of panhypopituitarism, the values for the 17-hydroxysteroids and 17-ketosteroids excreted in the urine are essentially zero, the uptake of radioactive iodine (I^{131}) is extremely low, and the urine does not contain any gonadotropin. In cases of anorexia nervosa, the amounts of gonadotropin, 17-ketosteroids and 17-hydroxysteroids in the urine may be low, but these substances are not absent.

Contrary to many of the descriptions in older textbooks, a majority of patients with panhypopituitarism are not extremely emaciated, whereas the patient is extremely emaciated in the characteristic case of anorexia nervosa. It is probable that many of the patients formerly classified as having Simmonds' disease actually had anorexia nervosa.

A physician who encounters a patient with acute postpartum necrosis of the pituitary may be faced with an acute problem of *treatment*, particularly the treatment of adrenal insufficiency. If this should occur, the management is the same as that which one would use in cases of an addisonian crisis.

For long-term maintenance therapy of panhypopituitarism, one will have occasion to administer moderate doses of extrapituitary hormones. Sufficient estrogen and testosterone should be administered to produce desired effects in the male and female respectively. It often may be desirable to administer small doses of testosterone or similar materials to females in order to produce a normal growth of axillary and pubic hair, as well as to aid and abet libido. Thyroid is administered in doses sufficient to eliminate the signs of hypothyroidism, but it should not be administered in doses large enough to produce toxic effects. Patients with panhypopituitarism may be unusually sensitive to the effects of thyroid preparations. Consequently, the dose of these preparations should be increased very slowly.

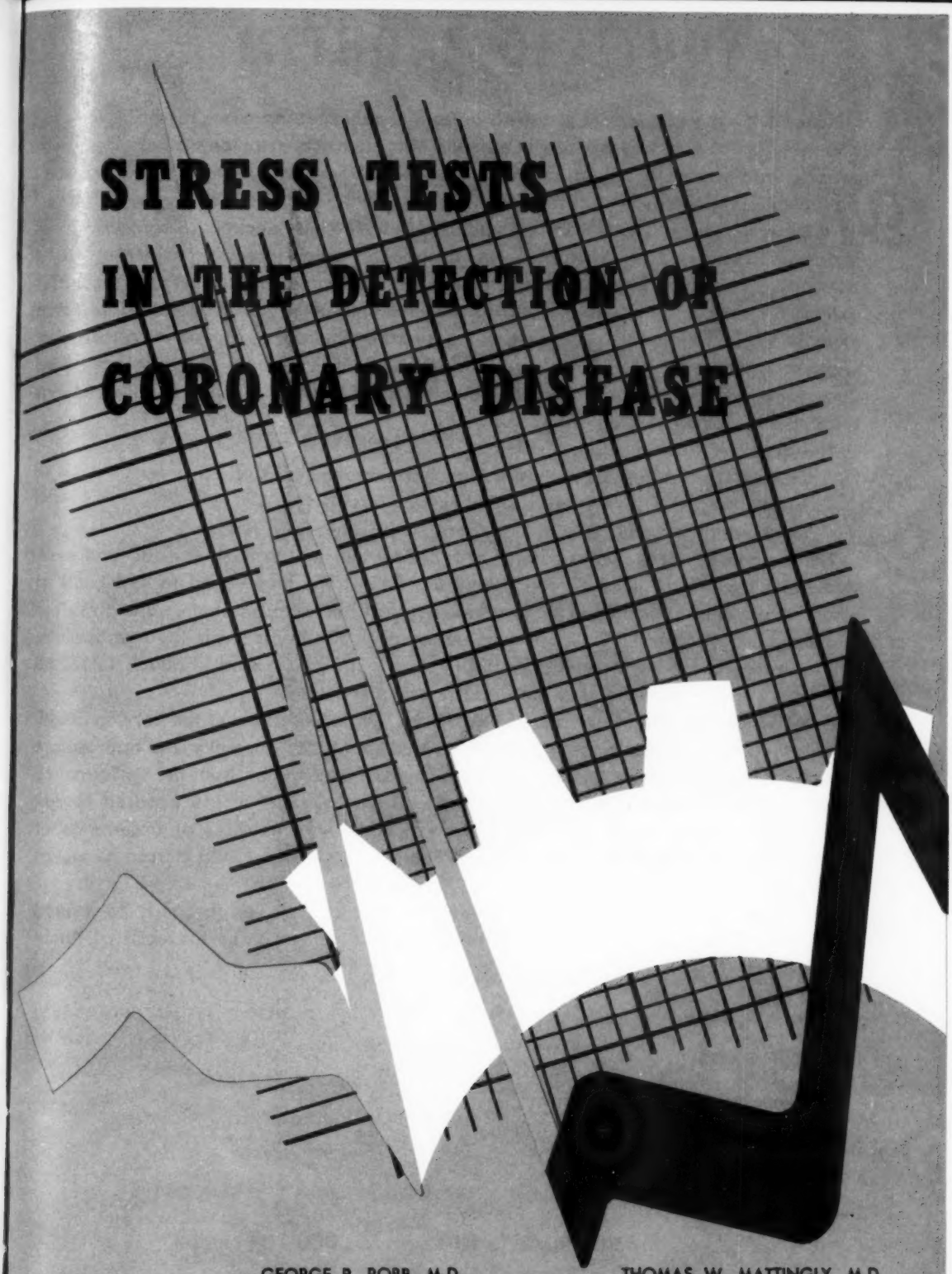
The doses of cortisone required for maintenance therapy in cases of panhypopituitarism are much smaller than the doses required for maintenance therapy in cases of Addison's disease. In my experience, the daily administration of 5 to 15 mg. has been adequate. Desoxycorticosterone is rarely required. In cases in which it is necessary, it should be used very cautiously. Progressive hypernatremia, edema, hypertension and convulsive seizures have been observed in patients who have been treated injudiciously with this preparation.

One may summarize all of the foregoing statements by saying that the patient with panhypopituitarism is one who lacks the normal system of endocrine checks and balances, and who, therefore, is hypersensitive to essentially all endogenous and exogenous stimuli, including the hormones.

In cases in which diabetes is associated with panhypopituitarism, the amount of insulin required is usually not more than 10 per cent of the amount required in the average case of diabetes. Since patients with panhypopituitarism are extremely sensitive to insulin, it must be used with great caution.

Grateful acknowledgment is made to the Schering Corporation for supplies of ethinyl estradiol and methyltestosterone and to the Upjohn Company for the supplies of testosterone cyclopentylpropionate which have been used in experimental, clinical and metabolic studies.

STRESS TESTS IN THE DETECTION OF CORONARY DISEASE



GEORGE P. ROBB, M.D.
HERBERT H. MARKS
Metropolitan Life Insurance Company
New York, New York

THOMAS W. MATTINGLY, M.D.
Walter Reed Army Hospital
Washington, D. C.

FOREWORD

One of the most important problems in both clinical and insurance medicine today is the detection of coronary disease in persons with equivocal symptoms or electrocardiographic evidence of impaired coronary circulation. These symptoms may be misinterpreted, and particularly in applicants for life insurance their significance may be minimized or they may not be reported in the medical history. While electrocardiographic stress tests have been used for more than two decades to obtain objective evidence on the adequacy of the coronary circulation, there is wide disagreement as to their value. This exhibit presents a clinical and statistical evaluation of the double standard two-step exercise test and of the anoxemia test, as measured by the rate of occurrence of coronary occlusion or of death from coronary disease subsequent to the test. The data are based upon long-term follow-up of persons virtually all of whom were for various reasons suspected of having coronary disease.

The purposes of these studies were:

To appraise the double standard two-step exercise and anoxemia tests

To test the validity of criteria for abnormal response

To compare the reliability of the exercise and anoxemia tests.

The material of these studies consists of *(1)* 836 military personnel, ages 30 and over, studied at the Walter Reed Army Hospital in 1942-1951, and traced to 1952, all of whom were given the double standard two-step test and 322 of whom were given the anoxemia test also; and *(2)* 493 persons applying for life insurance in the Metropolitan Life Insurance Company examined in 1949-March 1956 and traced to March 1957, all of whom were given the double standard two-step test only.

In follow-up studies of this kind, it is necessary to take into account the varying length of follow-up of individual cases and thus assure comparability of results. The appropriate unit of measurement is the sum of the person years of observation from the performance of the test to the end of the follow-up period, i.e., the years of life exposed to risk of the events under study. The results are expressed here as rates of occurrence of coronary occlusion and of death from coronary disease per 1,000 person years of observation.

The studies show that the double standard two-step exercise test, properly performed and interpreted, is a useful and practical method of detecting the presence of latent coronary insufficiency.

GEORGE P. ROBB, M.D.

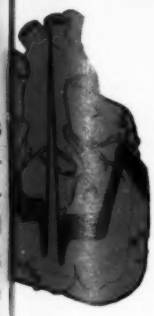
THOMAS W. MATTINGLY, M.D.
Walter Reed Army Hospital

HERBERT H. MARKS

Metropolitan Life Insurance Company

December 1957

This exhibit was first presented at the Annual Meeting of the American Medical Association, June 1957



METHODS OF STUDY

TEST PROCEDURES:

Exercise Test — Double Standard Two-Step Test only, standard two-step stairs and tables for number of ascents (Master).

Anoxemia Test — Levy Technique and apparatus.

Electrocardiograms

Before Exercise or Anoxemia: 12 conventional leads

After Exercise or During Anoxemia:

Walter Reed Army Hospital, 1942-1951

Bipolar limb leads I, II, III, and precordial leads V_4 or CF_4 made immediately, 3 and 8 minutes after completion of the exercise; during anoxemia at 5 minute intervals up to 20 minutes.

Metropolitan Life Insurance Company, 1949-1956

Applicants Examined at Company's Home Office

Leads I, II, III, and $V_{3, 4, 5, 6}$ and often aV_L and aV_F, made immediately after exercise and at 2 minute intervals thereafter to 10 minutes or return of electrocardiogram to the preexercise state.

Applicants Examined Elsewhere

Leads I, II, III, V_4 and V_5, and recently V_6, made immediately and 2, 5, and 10 minutes after exercise.

INTERPRETATION OF TESTS

Initial Criteria for Positive Test, Applied Provisionally

Master — for Exercise Test

Levy — for Anoxemia Test

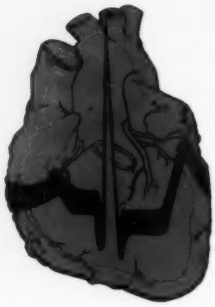
Subsequent Analysis by Type of Electrocardiographic Response

ST segment depression ST junction depression	T wave change	Arrhythmia Conduction defect

STATISTICAL EVALUATION

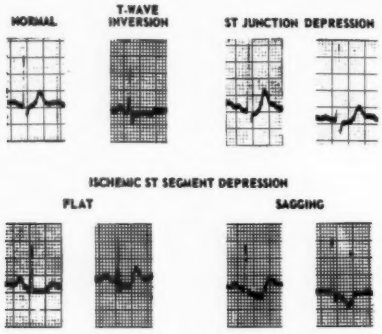
Rates per 1,000 person-years of observation

Deaths from all causes
Deaths from coronary disease
First occlusion subsequent to test



ELECTROCARDIOGRAPHIC RESPONSES TO DOUBLE TWO-STEP EXERCISE TEST

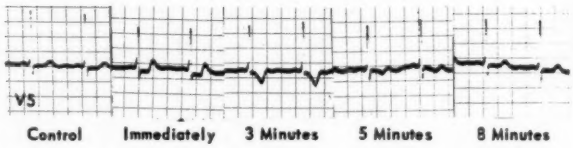
Basic Types



Serial Changes in ST Segment After Exercise

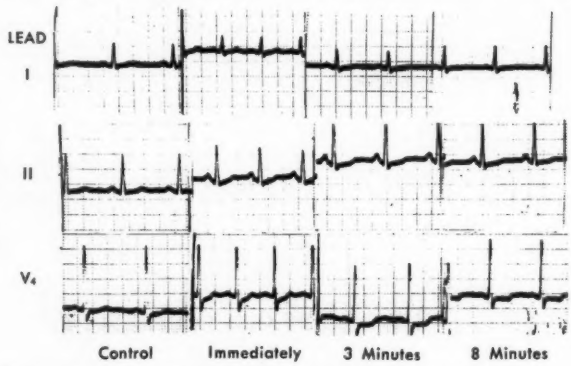
a. Coronary insufficiency with classical angina pectoris

48 year old female with six months history of angina, increasing in severity. Resting ECG, flattening of the ST segment in V_5 and V_6. Immediately after exercise, pronounced ST segment depression, ischemic in character. At 3 minutes, marked T wave inversion with less ST depression. Gradual return to control state in 8 minutes.



b. Detection of Coronary Insufficiency in Asymptomatic Subject

50 year old male with negative history and resting ECG was found on annual physical examination. Postexercise ECG showed ischemic ST depression. Eight months later developed severe pain in chest and arms while hunting; died five hours later in convulsive seizure (ventricular fibrillation). On autopsy, marked sclerosis of right coronary artery and occlusion from hemorrhage into a sclerotic plaque.

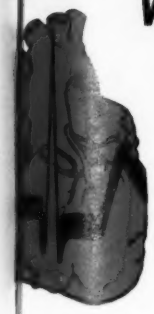


ST Segment Changes After Exercise in Various Precordial Leads

. . . shows need for multiple precordial leads

50 year old male evaluated *April 1955* because of angina. 12-lead resting ECG suggested possibility of old anteroseptal infarction, but inconclusive. Post-stress ECG showed ischemic ST segment depression. *September 1955*, extensive posterior wall infarction; slow recovery, with failure.

Basic types from Metropolitan Life Insurance Company. Case illustrations from Walter Reed Army Hospital.



Walter Reed Army Hospital Cases—

DESCRIPTIVE DATA

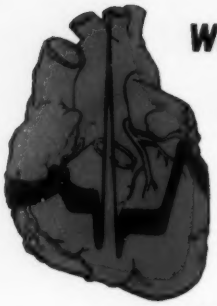
PRINCIPAL INDICATION FOR STRESS TEST

Indication	Percent of Total
Total	100.0
Chest pain or discomfort	70.0
a. Angina pectoris	8.3
b. Suspected coronary occlusion	5.6
c. Nonspecific	56.1
Myocardial infarction, healed documented	.6
ECG abnormality suggestive of coronary disease	13.8
a. Nonspecific ST and T wave changes	5.1
b. Bundle branch block	4.2
c. Healed myocardial infarction	.8
d. Other	3.6
Hypertension	4.5
Nonspecific cardio-respiratory symptoms	8.7
Other	2.4

AGE DISTRIBUTION OF CASES IN SELECTED CATEGORIES

	Percent of Total at All Ages			
		Abnormals		
			ST Depression	
Age at Test	All Cases	All Types*	Segment (Ischemic)	Junction
All Ages	100	100	100	100
30-39	21	17	14	24
40-49	36	39	31	36
50-59	34	35	44	31
60 +	8	9	10	10
Number of Cases	836	229	99	42

*According to Master's criteria.



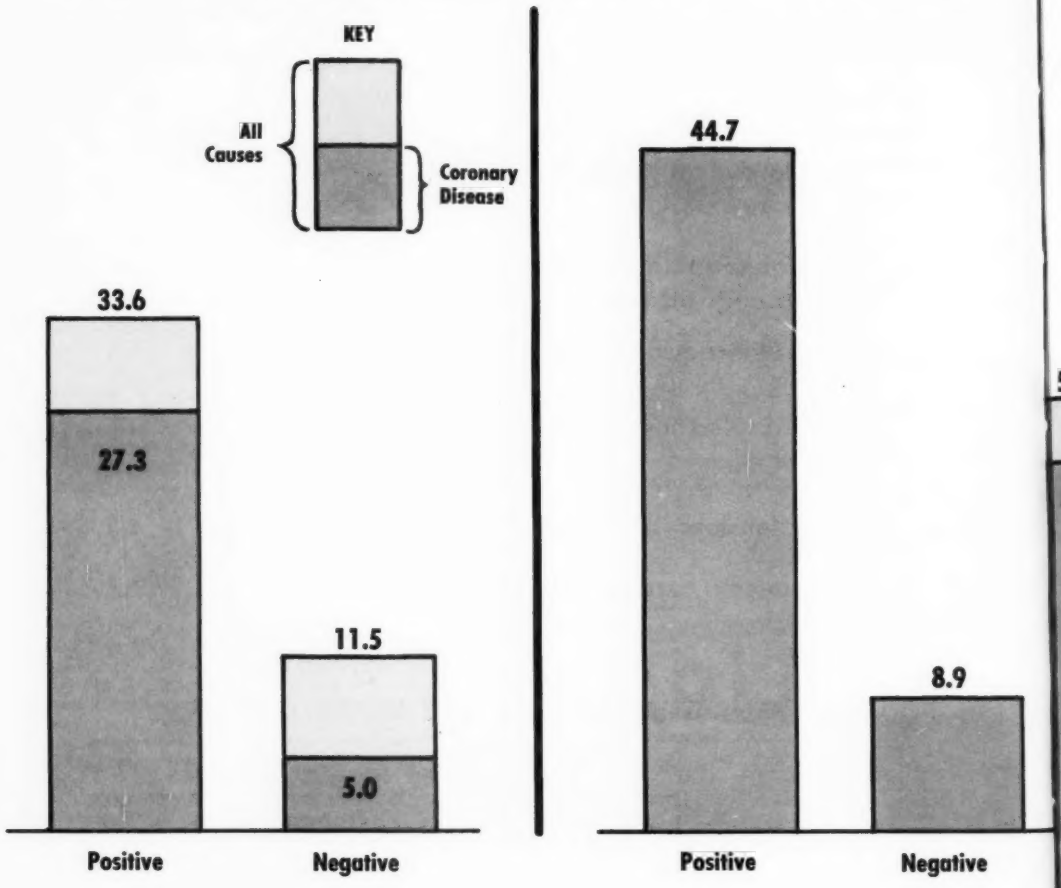
Walter Reed Army Hospital Experience

POSITIVE AND NEGATIVE REACTORS TO EXERCISE TEST*

Exercise Tests Performed in 1942-1951; Follow-up to 1952 Anniversary of Test

Death Rates
Per 1,000 Person Years of Observation

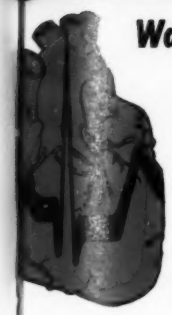
First Occlusion Rates
Per 1,000 Person Years of Observation



	POSITIVE	NEGATIVE
Cases	229	607
Deaths		
All Causes	43	39
Coronary	35	17
First Occlusions After Test	56	30

Double standard two-step exercise test only

*According to Master's criteria



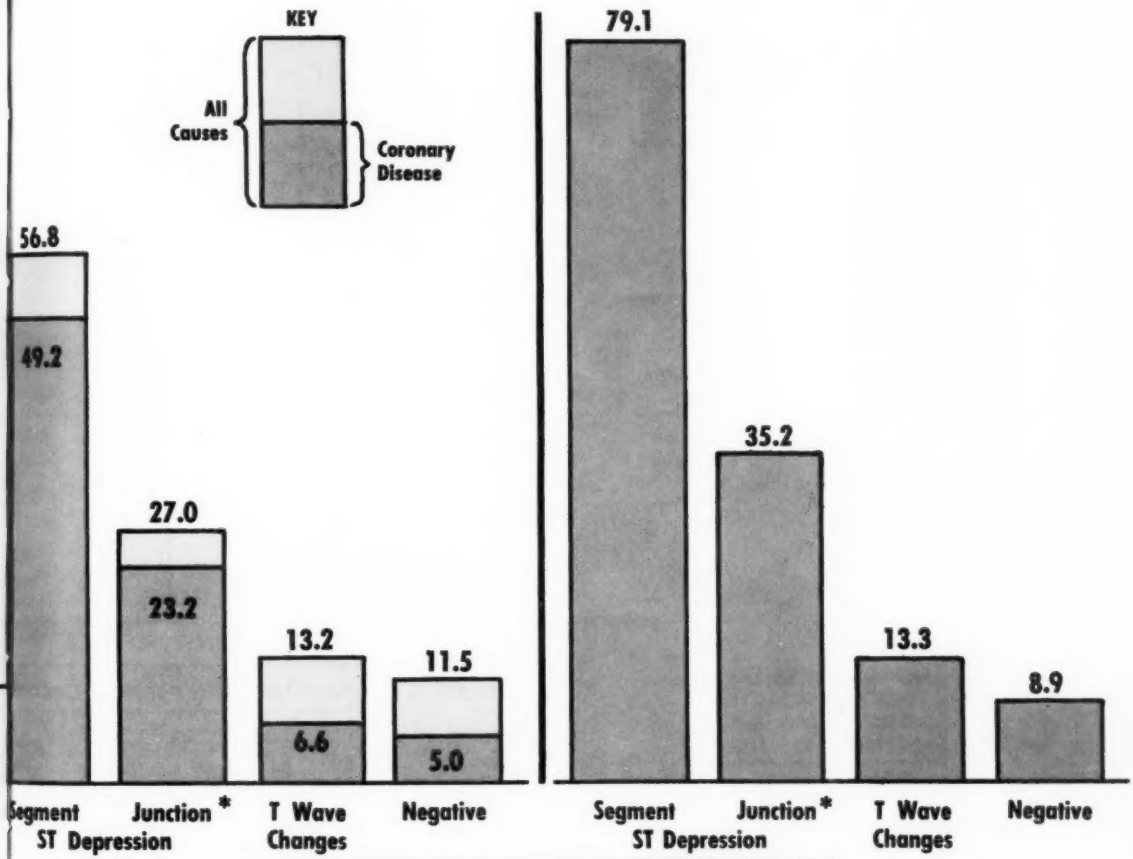
Walter Reed Army Hospital Experience

ST SEGMENT AND JUNCTION DEPRESSION, T WAVE CHANGE AND NEGATIVE RESPONSE TO EXERCISE TEST

Exercise Tests Performed in 1942-1951 ; Follow-up to 1952 Anniversary of Test

Death Rates
Per 1,000 Person Years of Observation

First Occlusion Rates
Per 1,000 Person Years of Observation

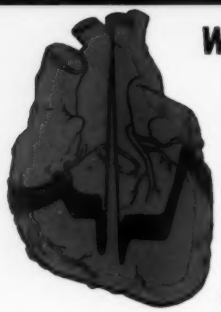


	ST DEPRESSION		T WAVE CHANGES	ARRHYTHMIA; CONDUCTION DEFECTS*	NEGATIVE
	SEGMENT	JUNCTION			
Cases	99	42	80	8	607
Deaths					
All Causes	30	7	6	—	39
Coronary	26	6	3	—	17
First Occlusions After Test	40	9	6	1	39

*Not shown in graph because of small size of experience.

udes indeterminate number of cases with myocardial ischemia in which ment depression was undetected because too few precordial leads were made.

Double standard two-step exercise test only

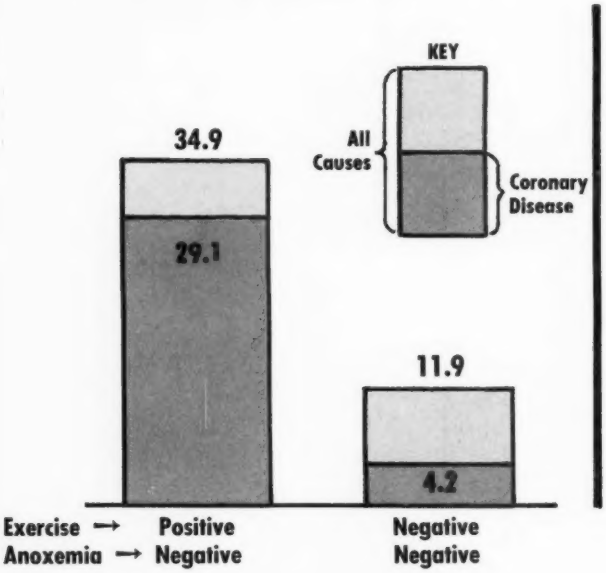


Walter Reed Army Hospital Experience

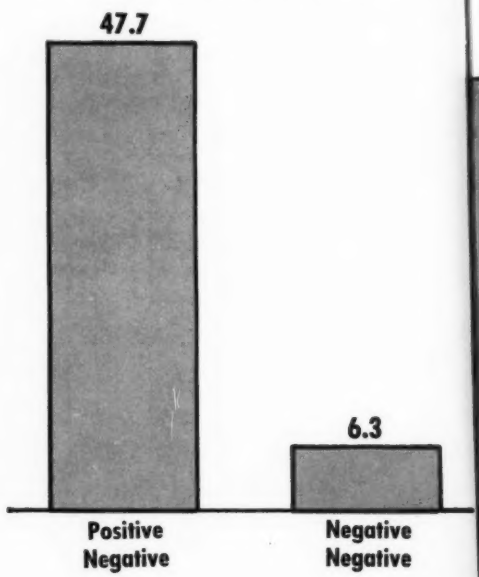
CASES WITH EXERCISE-POSITIVE ANOXEMIA-NEGATIVE TESTS AND WITH BOTH TESTS NEGATIVE*

Tests Performed in 1942-1951; Follow-up to 1952 Anniversary of Test

Death Rates
Per 1,000 Person Years of Observation



First Occlusion Rates
Per 1,000 Person Years of Observation



	EXERCISE-POSITIVE ANOXEMIA-NEGATIVE	EXERCISE-NEGATIVE ANOXEMIA-NEGATIVE
Cases	103	206
Deaths		
All Causes	24	17
Coronary	20	6
First Occlusions After Test	32	9

*Classified according to Master's and Levy's criteria for their respective tests.

ANOXEMIA TEST RESPONSE IN 81 CASES WITH ST DEPRESSION BY EXERCISE TEST

ECG RESPONSE TO ANOXEMIA	ECG RESPONSE TO EXERCISE			
	Segment Depression		Junction Depre	
	Number	Percent	Number	Per
Total Cases	59	100	22	1
Interpreted by Levy's Criteria				
Positive	10	17	1	
Negative	49	83	21	
Interpreted by ST Depression*				
Positive	26	44	3	
Negative	33	56	19	

*More than 0.5 mm.

17 of these 33 anoxemia test nega
had a coronary occlusion or died
coronary disease up to September

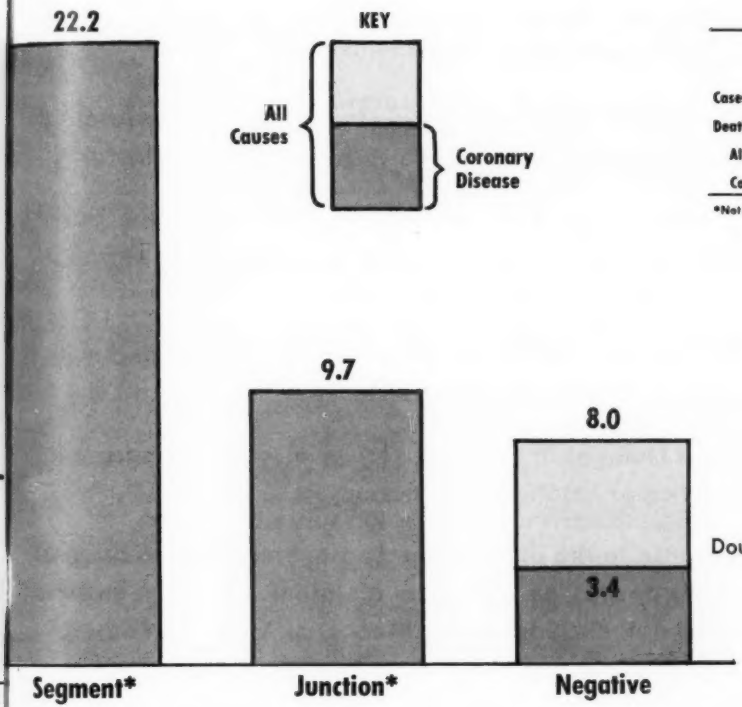
Experience of Metropolitan Life Insurance Company on Applicants for Insurance

APPLICANTS CLASSIFIED BY RESPONSE TO EXERCISE TEST

Tests Performed in 1949-March 1956; Follow-up to March 1957

Death Rates

per 1,000 Person Years of Observation



	ST DEPRESSION		T WAVE CHANGES*	NEGATIVE
	SEGMENT	JUNCTION		
Cases	106	81	17	288
Deaths				
All Causes	7	2	1	7
Coronary	7	2	1	3

*Not shown in graph because of small size of experience.

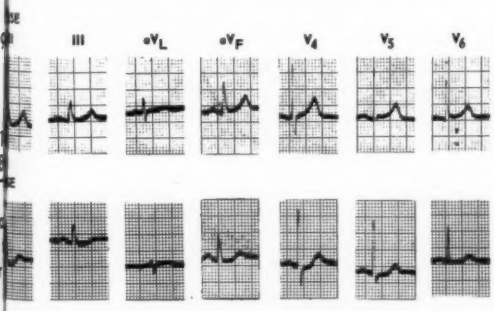
Double standard two-step exercise test only

*All deaths to date in these groups have been from coronary disease.

ILLUSTRATIVE PROBLEM CASES IN STUDY

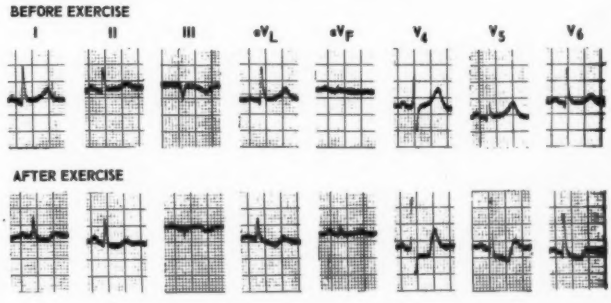
ISCHEMIC ST SEGMENT DEPRESSION AFTER DOUBLE TWO-STEP EXERCISE TEST

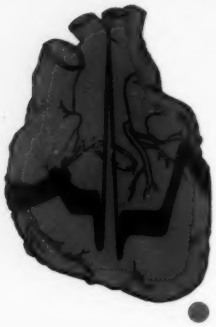
Coronary occlusion 5 weeks after test



ISCHEMIC ST SEGMENT DEPRESSION AFTER DOUBLE TWO-STEP EXERCISE TEST

Coronary occlusion and death 15 months after test





CONCLUSIONS

- A reliable stress test of the coronary circulation should impose sufficient stress to produce detectible myocardial ischemia in the presence of coronary narrowing with latent coronary insufficiency, but a normal response when the coronary circulation is adequate. For practical reasons, the technique of the test and the amount of stress should be standardized.
- The double standard two-step exercise test, properly performed and interpreted, seems to meet these requirements satisfactorily.
- The only reliable evidence of coronary insufficiency in the post-exercise electrocardiogram was found to be ischemic ST segment depression exceeding 0.5 mm. in any lead.
- Transitory ST junction depression after exercise associated with tachycardia is usually a normal finding.
- Isolated T wave changes in the postexercise electrocardiogram is not valid evidence of coronary insufficiency.
- A normal response to the double two-step exercise test excludes, for practical purposes, the presence of latent coronary insufficiency. It does not exclude the presence of coronary atherosclerosis.
- The anoxemia test was found to be unreliable in the detection of latent coronary insufficiency.

Further investigation of the validity of these findings is desirable. Accordingly, these studies are being continued in order to obtain more extended observations on a larger number of cases based on up-to-date electrocardiographic technique.

ESSENTIALS FOR SATISFACTORY PERFORMANCE AND INTERPRETATION OF THE EXERCISE TEST

PERFORMANCE

Standard amount of exercise (double standard two-step test)

Postexercise electrocardiograms . . .

. . . enough leads to record all significant electrical activity of left ventricular wall and septum

. . . frequent enough tracings to record significant changes

Precise performance of standardized procedure

Personal supervision of test by physician experienced with procedure

INTERPRETATION

— Criteria Based Upon This Study

Evidence of coronary insufficiency (Positive Test)

Ischemic ST segment depression exceeding 0.5 mm. in any lead*

No evidence of coronary insufficiency (Negative Test)

No significant change

Transitory ST junction depression

Isolated T wave change

Changes of doubtful or unknown significance

ST segment depression less than 0.5 mm.

Prolonged ST junction depression with some flattening of ST segment

Arrhythmias

Conduction abnormalities

*Valid except in presence of (1) digitalis medication, (2) use of other drugs causing ECG deformity, and (3) hyperventilation.

Note: Ischemic ST segment depression, a term used by Paul J. Wood, refers to a flattening and horizonal or sagging depression of the ST segment, induced by exercise or occurring spontaneously, which denotes myocardial ischemia.

TECHNIQUE OF THE DOUBLE STANDARD TWO-STEP EXERCISE TEST USED BY THE METROPOLITAN LIFE INSURANCE COMPANY

Based Upon the Instructions to Physicians Performing the Test for the Company

The procedures must be carried out exactly as described. The test is to be done only under the personal supervision of a physician experienced in its use. Before the test is performed, at least one hour should elapse after smoking or ingesting food or cold drink; one week should elapse after a cold or other infection, and three weeks after medication with digitalis.

Do not carry out the test if the preliminary resting ECG shows evidence of acute coronary insufficiency or recent myocardial infarction. Stop the test at once if during the exercise the subject develops cardiac pain or other serious symptom, except dyspnea or leg fatigue, or if evidence of distress is observed. Have him lie down and make the postexercise ECG's as specified below. Keep the subject under observation until the reaction is over.

A. NECESSARY EQUIPMENT:

(1) Standard two-step stairs.

(2) Direct-writing electrocardiograph, that makes tracings with distinctly inscribed deflections and segments.

(3) Stop watch, or watch (or clock) with a seconds sweephand.

(4) Suction electrodes for precordial leads.

(5) Table showing appropriate number of ascents for double two-step test.*

B. PROCEDURES:

(1) Locate precordial V_1 to V_6 positions accurately; mark them clearly on chest wall.

(2) Make preliminary 12-lead ECG in supine position, for detection of acute coronary insufficiency or recent myocardial infarction and as reference for postexercise ECG's. Unplug the 4-lead cable from electrocardiograph during performance of exercise but leave lead wires attached to subject.

(3) Have subject complete prescribed number of ascents in exactly three minutes by stop watch or clock. The subject then lies down immediately, relaxes completely, and breathes lightly or holds his breath while each lead is being made.

(4) Make postexercise ECG's by stop watch immediately, and 2, 4, 6 and 10 minutes after exercise, and when indicated, at 5 minute intervals thereafter until tracing has returned to preexercise state. Complete "immediate" postexercise ECG within 2 minutes after end of exercise.

(5) Use enough leads in the postexercise ECG's to cover major electrical fields of heart. Routinely use Leads V_6, V_5, V_4, V_2, aV_R, aV_L, and aV_F, made in that sequence.

(6) Make each lead at least 6 inches long. Each lead should contain 5 consecutive cycles having deflections and segments suitable for interpretation.

(7) Prevent or minimize technical defects:

Poor Definition — Avoid indistinct or smudged deflections and segments by proper heating of the stylus.

Wandering or Drifting of Base Line — Prevent by vigorous rubbing of skin under electrodes with electrode jelly, by keeping electrical contacts clean and by shallow respiration or apnea by subject during inscription of ECG's.

Somatic Tremor — Prevent by relaxation and avoidance of toe pointing.

Electrical Interference — Eliminate by adequate grounding.

*Master, Friedman and Dack, American Heart Journal, 24:777, December 1942.

CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Case Report

A 59 year old white man was first admitted to Hines Veterans Administration Hospital in July 1954 with complaints of weakness and pain in the epigastrium associated with sweating. He had worked as a postal employee until two and one-half days before, when these symptoms, which had begun about a month earlier, became more severe and the epigastric pain extended into the chest.

Blood pressure was 80/60 but the patient was not in distress. An electrocardiogram was reported as probably normal. The blood sugar level varied from 384 to 105 mg. His diabetes was very erratic and difficult to control. While in the hospital the patient complained of pain in the left lower abdominal quadrant, which was found to be associated with diverticulosis of the descending and sigmoid colon. He was discharged in September 1954.

He returned to the hospital in a few weeks because of pain in the left lower part of the abdomen, increasing weakness, loss of appetite, and a 7 lb. weight loss in three weeks: his diabetes was uncontrolled. The abdominal pain was constant and dull, did not radiate, and was getting worse. Blood pressure on admission was 112/70. The fasting blood sugar level was 350 mg., and urinalysis revealed 3 plus sugar and no acetone.

A diabetic diet was prescribed and the patient received 45 units of NPH insulin each morning. The abdominal discomfort continued despite administration of phenobarbital and tincture of belladonna. A barium enema study again revealed diverticulosis, and stools persistently contained occult blood (4 plus).

After the diabetes was again controlled (35 units NPH insulin and 12 units regular insulin given every morning), a surgical consultation was held and the patient was transferred to the surgical service on November 10, 1954. Twelve days later an abdominal exploratory operation and transverse colostomy were done. Multiple diverticula of the sigmoid were found, none with induration. On January 10, 1955, abdominal exploration was again performed and the bowel examined, but resection was not done. Seventeen days later the

transverse colostomy was dissected from the anterior abdominal wall and the transverse colon reanastomosed. The wound became infected, requiring opening of the incision. This finally cleared and the patient was discharged on February 23, 1955. He returned for follow-up examinations in April and October 1955 and in April 1956.

On October 10, 1956, the patient was brought to the hospital in an ambulance. He was emaciated, semicomatose, confused and dehydrated, and was holding his abdomen as if in severe and constant pain. There was an acetone odor to his breath. Blood pressure was 55/0, pulse 120, respirations 32, and temperature 95.6° F. Shortly after admission, he vomited coffee-ground material. His wife stated that the present condition had begun about 24 hours before admission with polydipsia, polyuria, nausea, vomiting and lapse into a semicomatose state.

Urinalysis revealed sugar and acetone, both 4 plus. The blood sugar level was 348 mg., the carbon dioxide-combining power 13. Administration of saline solution was started immediately, with regular insulin added at intervals until the amount of sugar in the urine decreased and acetone disappeared. The red blood cell count was 4,900,000 on admission with 15 gm. hemoglobin; the white blood cell count was 14,750 with 81 neutrophils. Repeated blood counts showed red blood cell counts of 4,000,000 and 3,500,000 with 13 gm. hemoglobin and 9100 white blood cells. Later the same day the carbon dioxide-combining power was 24.2, the level of chlorides 113 mg., and blood sugar 396 mg. After 18 hours' treatment the carbon dioxide-combining power was 26.8 and the chloride level 112 mg. Serum amylase was 13.6 mg. An electrocardiogram was abnormal, with low voltage and electrolyte imbalance. Serum sodium was 139 mg., potassium 4.2 mg.

Physical examination on admission gave essentially normal findings. The abdomen was generally soft and slightly tender but without rigidity or masses. Blood pressure rose slightly to 70/20 but no higher. As treatment of the acidotic state continued, the abdominal discomfort lessened. A Levin tube was passed, and suction yielded about 1500 cc. of coffee-ground material; no bright-red blood was obtained. As the day of admission went on, the results of laboratory tests improved but the patient's general condition did not. He remained semicomatose. He received 6000 cc. of saline and was therefore digitalized. He vomited more coffee-ground material and complained of abdominal pain. He died early on October 11, about 20 hours after admission.

Discussion and Differential Diagnosis

DR. EDWARD O. WILLOUGHBY (assistant chief, medical service): I have been asked to discuss this case in 25 minutes. The time suggested is a little unfortunate, because if one knew the diagnosis about five minutes would suffice; if one did not, it would take at least an hour to confuse the audience.

This 59 year old white man had three major admissions and three follow-up admissions to the hospital over a period of 28 months. When he was first admitted in 1954 he complained of weakness, epigastric pain and sweating. These symptoms had begun about a month before and progressed in severity with the pain radiating into the chest. Blood pressure was 80/60. We are not told what the pulse rate was; I would suspect that the patient might have been in some degree of shock with a rapid pulse. In the report of his first hospitalization the blood pressure is not mentioned again. The protocol states that the patient was not in distress; however, persons in shock may not complain of pain. Blood sugar varied from 384 to 105 mg., establishing the diagnosis of diabetes mellitus. He received insulin, and the pain in the left lower abdominal quadrant was investigated. At first the pain was epigastric, radiating into the chest; later it was in the left lower quadrant and found to be associated with diverticulosis of the descending and sigmoid colon.

The finding of diverticulosis in the bowel by no means indicates that the patient had diverticulitis. My x-ray colleagues say that they sometimes can distinguish between the two. The initial epigastric pain radiating into the chest, the low blood pressure, and the

"probably normal" electrocardiogram are quite compatible with a diagnosis of myocardial infarction. The patient's temperature, sedimentation rate, white blood cell count and differential are not mentioned, and I assume these were normal.

He returned to the hospital shortly after discharge, with uncontrolled diabetes, pain in the left lower abdominal quadrant, increasing weakness, loss of appetite, and a 7 lb. weight loss in three weeks. The abdominal pain was constant, dull and nonradiating and was getting worse. Blood pressure was normal, fasting blood sugar was high, and there was glycosuria but no acidosis. Diabetic management was instituted, but the abdominal discomfort did not disappear with control of the diabetes. A barium enema study was repeated. The stools persistently contained occult blood (4 plus). Diverticulitis may cause this; of course, occult blood raises extensive possibilities in differential diagnosis. Was he on a meat-free diet at the time? Transverse colostomy was done although the diverticula of the sigmoid were not inflamed and presumably were not causing obstruction.

A couple of months later, abdominal exploration was again performed and nothing significant was found. The transverse colostomy was later closed, and the patient was discharged in February 1955. Details of the follow-up examinations in April and October 1955 and April 1956 are not furnished, and apparently the patient was doing fairly well.

The terminal hospitalization covered a very short period, beginning October 10, 1956. His condition had all the earmarks of a rapid onset of diabetic coma, with shock and hematemesis. He was holding his abdomen as if in severe and constant pain. There was an acetone odor to his breath. Blood pressure again was quite low; pulse and respirations were rapid, and temperature was subnormal. He had symptoms of uncontrolled diabetes progressing to coma. With treatment the red blood cell count went from 5,000,000 to 3,500,000, the hemoglobin from 15 to 13 gm., and the white blood cell count from 14,750 to 9100. The carbon dioxide-combining power went up: the sugar in the urine dropped: the acetone disappeared from the urine. Potassium was normal, and serum sodium nearly normal. With energetic treatment he responded well as far as laboratory studies were concerned, but he did not respond well clinically—another case in which laboratory findings improve but the patient does not. I think he had excellent treatment for his diabetes.

The cause of the catastrophic terminal episode was sought. They considered pancreatitis. The amylase was 13.6, which is normal. Potassium was normal. The statement was made that "he received 6000 cc. of saline and was therefore digitalized." I wish to assure everyone that we do not digitalize anybody just because he receives a certain amount of saline. He had a soft abdomen; slight tenderness can be disregarded because of the patient's general physical state; there was no rigidity, and masses were not palpable. We are not told what the bowel sounds were at that time. The course continued downhill, and the patient vomited more coffee-ground material. Coffee-ground material was aspirated from the stomach and the patient continued to complain of abdominal pain. He died about 20 hours after admission.

There are three facets to consider: (1) The patient was a 59 year old white man with diabetes mellitus; (2) he had abdominal pain which was persistent and severe and, most important of all, as far as possibly giving a clue to diagnostic considerations, three laparotomies presumably did not disclose the cause of the abdominal pain; (3) he had a terminal catastrophe which probably precipitated diabetic acidosis, shock, severe abdominal pain and hematemesis. The whole course covered about 28 months and the terminal acute episode less than 24 hours.

Relatively few patients nowadays die in diabetic coma as a primary cause (table 1). Three-fourths of diabetic patients die with involvement of blood vessels as the primary cause—in the brain, kidneys, heart or elsewhere. About 6 per cent die of infections. About 10 per cent die of cancer, and it is said that cancer of the pancreas is very common in diabetic persons. Suicides, accidents, tuberculosis, insulin reactions, etc. make up the re-

TABLE 1

CAUSES OF DEATH OF 656 DIABETIC PATIENTS, 1950-52;* EXPERIENCE OF JOSLIN CLINIC, BOSTON, MASSACHUSETTS

CAUSE OF DEATH	NUMBER	PER CENT OF ALL CAUSES
All causes	656	100.0
Diabetic coma (primary)	7	1.1
Cardiorenal-vascular	498	75.9
Arteriosclerotic	496	75.6
Cardiac	312	47.6
Coronary and angina	234	35.7
Renal, total	85	13.0
Diabetic nephropathy	61	9.3
Typical or unqualified†	54	8.2
Probable	7	1.1
Cerebral	83	12.7
Gangrene	7	1.1
Site unassigned	9	1.4
Other circulatory and rheumatic heart disease	2	0.3
Infections, total	38	5.8
Pneumonia and respiratory	26	4.0
Gallbladder	1	0.2
Appendicitis	1	0.2
Kidney, acute	4	0.6
Abscesses	1	0.2
Other infections	5	0.8
Cancer	63	9.6
Tuberculosis	6	0.9
Diabetes (i.e., unknown)	6	0.9
Accidents	12	1.8
Suicides	3	0.5
Insulin reactions	1	0.2
Other diseases	22	3.4

*Deaths reported through April 7, 1952.

†Confirmed by autopsy.

(From JOSLIN, E. P., ROOT, H. F., WHITE, P. and MARBLE, A.: The Treatment of Diabetes Mellitus. Ed. 9. Philadelphia. Lea & Febiger, 1952, p. 187.)

mainder of the list of causes of death among diabetic patients.

Table 2 lists the causes of death associated with coma. Uncomplicated coma was the cause in 12 of the 46 cases represented—some 25 per cent, which Joslin prefers to call "needless deaths." These patients died because of inadequate recognition or inadequate treatment of the diabetic coma; so that even in this day and age there still is, percentagewise, an appreciable number of deaths from diabetic coma. Infection caused 26 of the 46 deaths, and included septicemia, renal abscesses, acute pancreatitis and pneumonia. Coronary occlusion, pulmonary emboli and infarcts, and miscellaneous causes—unexplained alkalosis is an intriguing one—accounted for eight of the deaths.

Returning to the severe abdominal pain in this case, the cause of which was not established on repeated laparotomy, referred pain from nerve roots, spinal cord, epidural abscesses, spinal abscesses, tabes dorsalis—all are quite unlikely. One should always think of acute intermittent porphyria in cases of abdominal pain. A Watson-Schwartz test of the urine might have been helpful. The color of the urine was not mentioned, nor were neurologic findings or mental symptoms other than the semicomatose state. Sickle cell disease and Schoenlein-Henoch purpura may cause abdominal pain; they are unlikely in this case.

The patient was a white man, there is no evidence that a sickling preparation was made, and there was no purpura or joint involvement. Lobar pneumonia with diaphragmatic pleurisy causes abdominal pain.

Abdominal pain is a prominent symptom in diabetic acidosis, possibly in 40 per cent of the cases. It may be so severe as to mimic intra-abdominal disease, and one would not know whether a patient had appendicitis or some other intra-abdominal inflammation and then went into acidosis or whether he had primary diabetic acidosis with the resultant abdominal pain. Good surgical judgment is necessary, and the question often is resolved by a few hours of vigorous antidiabetic coma treatment. The cause of the abdominal pain in diabetic coma is going to be considered; however, it is associated with dehydration, sodium balance, acidosis, and one may hear a pleural rub which disappears with hydration of the patient. It has been suggested that there is necrosis of the peritoneal cells due to acidosis and dehydration, which may produce the peritoneal irritation.

Renal cortical necrosis is very rare. It is found mainly in pregnancy with severe blood loss, which, of course, this man did not have. Few cases have been reported in which the syndrome of renal cortical necrosis has occurred in men or nonpregnant women, and the clinical picture was one of sudden abdominal pain, vomiting and diarrhea. The anuria may be delayed a few days. Some patients have flank pain, some do not. Often this follows tonsillitis or an upper abdominal catastrophe such as perforated peptic ulcer, acute pancreatitis or abdominal trauma. This would not account for such chronic abdominal pain.

A lymphoma involving the mesentery, the small bowel, etc. would not have been missed at operation. It is unlikely but possible for a retroperitoneal tumor to be symptomatic but not obvious at operation. It is difficult to distinguish between carcinoma of the pancreas and pancreatitis at the time of laparotomy. Both diseases are fairly frequent among diabetic patients, and actually pancreatitis may cause diabetes. The normal blood amylase level does not rule out pancreatitis. There is nothing to point to gallbladder disease. The patient might have had gastric mucosa in a Meckel diverticulum with the abdominal pain due to an ulceration, going on to eventual perforation and peritonitis. Carcinoma of the stomach and peptic ulceration of the stomach and duodenum with perforation are possibilities, but there is nothing to point to them.

Could he have had an aneurysm of the aorta? It is unlikely, I believe, that the surgeons would have missed a large aneurysm. Dissecting aneurysm may be somewhat more attractive as a possibility. If it were located in the upper abdominal aorta, it could have dissected both upward and downward at various times. It might well have been missed on physical examination, it might well have been missed at the three laparotomies, it could well have dissected and bled into the peritoneal cavity and precipitated acidosis, and it certainly could have caused death. I think it is a very attractive possibility. I cannot say anything more in favor of or against it.

However, looking at tables 1 and 2 one sees the tremendous amount of arteriosclerosis involved in deaths of diabetic patients, and I wonder if this patient possibly could have had stenosis of the superior mesenteric artery, a stenosis that allowed enough blood to flow into

TABLE 2

DIABETIC COMA; CAUSES OF DEATH IN 46 AUTOPSIED PATIENTS DYING BEFORE HOSPITAL DISCHARGE (ONE HOUR TO 63 DAYS AFTER ADMISSION)

	CASES
Coma, uncomplicated	12
Septicemia following local infections (Neck, 4; labium, 3; kidney, 2; appendix, 1; foot, 1; mastoid, 1; prostate, 1; sinuses, 1)	14
Multiple renal abscesses (septicemia not proved)	2
Acute pancreatitis	3
Pneumonia	7
Other causes (1 case each with pulmonary embolism, infarct of lung with empyema, hemorrhage from duodenal ulcer, cerebral softening, and unexplained alkalosis; 3 from coronary occlusion)	8

(From JOSLIN, E. P., ROOT, H. F., WHITE, P. and MARBLE, A.: The Treatment of Diabetes Mellitus. Ed. 9. Philadelphia, Lea & Febiger, 1952, p. 365.)

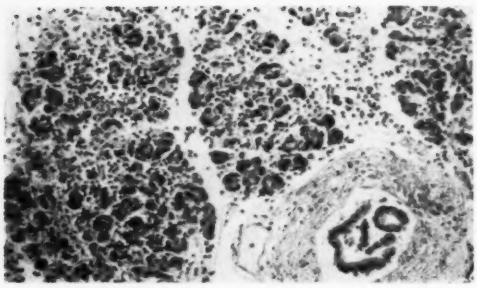


FIGURE 1. Photomicrograph of pancreas showing infiltration with inflammatory cells throughout. There is no hemorrhage present.

the intestines to keep them alive, that would not produce an infarction at the time of laparotomy, but that would produce abdominal pain which certainly could be lower in the abdomen or could be epigastric, and then after a period of time (some 28 months) if he finally might have had an occlusion, with infarction of the bowel, gangrene, peritonitis, shock, and death in diabetic coma. Julius Bauer has described this much as I have. He has stated that the attacks may last from a few minutes to several hours and may be extremely severe. Patients may refer to the pain as "gas." Often it is described as boring, and sometimes as colicky. It is analogous to angina pectoris and intermittent claudication in the legs. It often is precipitated by a heavy meal, especially if the patient walks following the meal.

My diagnoses are (1) diabetes mellitus, with diabetic coma, and (2) thrombosis of the superior mesenteric artery, causing infarction of the small bowel and peritonitis.

RADIOLOGIST: A number of x-ray examinations were done, all of which were essentially negative except for those of the colon. A barium enema study demonstrated diverticula in the region of the sigmoid and the descending colon. There were diverticula along the lateral border of the sigmoid and the descending colon. There was no narrowing in the region of the involved colon; the mucosal folds appeared normal. All these findings would preclude diverticulitis, and the most that could be said is that this was a diverticulosis of the sigmoid and probably the descending colon.

QUESTION: How do you rule out diverticulitis entirely in this case?

RADIOLOGIST: In diverticulitis there usually is persistent narrowing in the area of the diverticula—it is more than spasm, it is an actual narrowing. The sigmoid colon filled out well in this case. In diverticulitis this area would be persistently narrowed and one would see widening and distortion of the folds, which were not present here. Sometimes in diverticulitis one sees perforation, with a fistula, and none of the barium enemas gave any evidence of a fistula or a mass surrounding the diverticula. That is why we called this just diverticulosis without signs of diverticulitis.

DR. LERNER (senior resident, general surgery): One thing that was not dwelt on was the 1500 cc. of coffee-ground material in this man's stomach. The patient complained of pain in the epigastrium of a month's duration, pain which did not become really severe until two and a half days before his admission to the hospital. I assume he came in as an emergency. There is no explanation of the patient's abdominal condition except that he complained of severe epigastric pain. The diabetes was well controlled.

The second admission was not an emergency. The patient came in as a diabetic and was handled as a diabetic, apparently coming in voluntarily, about three weeks after discharge, because of a 7 lb. weight loss in three weeks. However, he did have 4 plus blood in the stools. The diabetes was controlled. An exploratory abdominal operation on the basis of the barium enemas describing the diverticula, the condition being described as diverticulosis by x-ray, was performed. The surgeons found that the diverticula were not indurated, not inflamed, and I do not know why transverse colostomy was done. Certainly one would think it would be done to give the bowel a chance to rest. Two months later the bowel again was examined at operation, but resection was not performed.

I wonder if, at the time of the second exploration, they went back to check the small bowel once again and the stomach, and possibly the pancreas. Here we had a known severe diabetic, and many times in such cases there

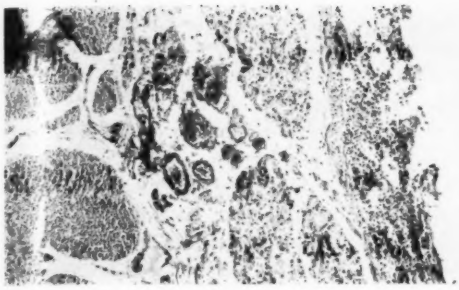


FIGURE 2. Photomicrograph of stomach showing superficial erosions, inflammatory cell infiltration, and numerous dilated submucosal vessels.

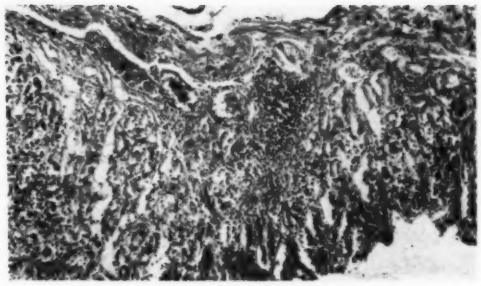


FIGURE 3. Photomicrograph showing hemorrhage in the submucosa with many dilations and some erosion.

may be some pancreatic insult, and I wonder if they were trying to determine the state of the pancreas at that time, since chronic pancreatitis and carcinoma of the pancreas are very difficult to differentiate.

The last admission to the hospital was an emergency; the man definitely was in shock, with epigastric pain, although the abdomen was soft and only slightly tender, with no rigidity. The serum amylase was determined only once, and it was normal; this was during his final hospitalization, and of course serum amylase is not always consistent with the picture of pancreatitis. I was impressed with the coffee-ground material removed from the stomach. I felt that, aside from the diabetes mellitus, this man might have had either a bleeding ulcer or a pancreatitis wherein there was some digestion of the lumen of the stomach, which would produce the coffee-ground material.

I am overlooking the one serum amylase determination that was normal, and impressing myself only with the idea that in a case of diabetes of such severity, with this acute pain in the midepigastric region, I think the man had pancreatitis—pancreatitis with digestion of the gastric mucosa causing the coffee-ground vomiting.

DR. WILLOUGHBY: I did not discuss the differential diagnosis of upper gastrointestinal bleeding as fully as I might have. I did not feel it was likely that the man had an upper gastrointestinal ulceration lasting over this period of time and being missed. I mentioned a number of other possible causes, many of which would explain the terminal hematemesis: aneurysm rupturing into the gastrointestinal tract, Meckel's diverticulum, thrombosis of the mesenteric artery. Pancreatitis is not a prominent cause of massive hematemesis.

DR. LIONEL BERNSTEIN (section chief, gastroenterology): Was it shown that he ever did have an upper gastrointestinal series?

DR. MYRON E. RUBNITZ (chief, laboratory service): One was done but it did not show anything abnormal.

Postmortem Findings

The body weighed about 110 lb. Pertinent autopsy findings were limited to the gastrointestinal tract. There was marked gastric dilatation with a large amount of coffee-ground material in the stomach and small erosions in the lower end of the esophagus, stomach, and first portion of the duodenum. The cause of death was thought to be massive gastrointestinal hemorrhage, concomitant with or due to diabetic acidosis and coma. Incidentally, there were more diverticula in the large bowel, and the areas of previous surgical intervention were well healed and did not show recent changes.

Microscopic section through the pancreas showed mild but diffuse infiltration of acute inflammatory cells with minimal parenchymatous changes and no associated hemorrhage (figure 1). This is in marked contrast to the picture seen in acute hemorrhagic pancreatitis with its severe destruction of tissue, and to

the acute suppurative pancreatitis characterized by masses of inflammatory cells.

Other sections of the pancreas showed histologic evidence of diabetes mellitus. Many of the islets of Langerhans were hyalinized, and some also demonstrated the acute inflammatory cell infiltrates in and around the islets. The histologic appearance of the islets correlates well with the five year history of diabetes in this case.

Sections through the stomach revealed superficial erosions of the mucosa with inflammatory cell infiltration and evidence of recent hemorrhage (figures 2 and 3). The latter finding was noted particularly about many of the dilated submucosal vessels; the hemorrhages were a result of the gastric dilatation.

The association of gastric dilatation and hemorrhage with diabetic acidosis and coma is often described. The mechanism remains obscure. Sections through the myocardium of the anteroseptal wall showed small foci of fibrosis. Recent evidence of infarction was not found. The myocardial fibers about these fibrotic areas showed only hypertrophy.

It is possible to correlate the focal myocardial fibrosis with the history of pain radiating into the chest a few years before. At one point in the anterior descending branch of the left coronary artery there was marked arteriosclerosis. We know that occlusion or even narrowing of the lumen at that point often is associated with myocardial infarction. However, grossly, infarction either old or recent was not found, so we may assume that this was merely a small isolated area.

The hemorrhage associated with the small erosions of the upper gastrointestinal tract is common in diabetic acidosis and coma, particularly in association with severe gastric dilatation. The small vessels become dilated and engorged and then rupture, with resulting hemorrhage. This patient, at the time of his death, had approximately 1500 cc. of coffee ground material in the stomach. Approximately that much was also taken from his stomach during the few hours prior to his death, and we do not know how much he vomited at home before admission to the hospital. Therefore, these hemorrhages certainly were not minor, although I do not think he died as a result of hemorrhage. Rather, the cause of death probably was the diabetic acidosis, aggravated if not caused by the recent acute interstitial pancreatitis.

It often has been stated that acute pancreatitis is too often overlooked in persons who are known to have diabetes. A recent report described eight patients with acute pancreatitis associated with diabetes in approximately 100 cases of acute pancreatitis; thus about 7 per cent of the patients with acute pancreatitis had associated diabetes. Of course this does not take into consideration the cases of severe acute hemorrhagic pancreatitis in which diabetes develops, a not too uncommon occurrence. But here is a patient with diabetes in whom pancreatitis developed.

DR. BERNSTEIN: How do you explain the normal serum amylase with pancreatitis?

DR. RUBNITZ: The serum amylase was low because of the mild inflammatory changes. Other than a little edema and color change, there was little else grossly to be found in the pancreas. Obviously the amount of functioning pancreatic tissue remaining was sufficient so that there was not a great deal of necrosis, merely a moderate infiltration of inflammatory cells.

For some reason, the excessively high mortality rate among diabetic patients has been mentioned in many reports and cannot be correlated with the anatomic lesions, which are not particularly severe. In one series of 12 cases, three patients died within 24 hours while over half were in shock.

CLINICAL STUDY

New Beneficial Agents in the Treatment of Acne Vulgaris and Seborrheic Dermatitis

DOWLING B. STOUGH, ROBERT A. LEWIS, BILLY L. FARMER, LAMAR S. OSMENT AND RAY O. NOOJIN*

Medical College of Alabama, Birmingham

DOWLING B. STOUGH

An abnormal sebaceous state is a frequently encountered dermatologic condition. The patient notices either an abnormally increased oiliness of the skin or an inflammatory involvement of the seborrheic areas. Acne vulgaris is often associated with increased activity of the sebaceous glands in the postadolescent or early adult stage. Correction of seborrheic dermatitis of the scalp is an important phase of the treatment of acne vulgaris. Successful treatment may prove difficult in some cases.

Although the causes of these conditions are not completely understood, more efficient and cosmetically acceptable therapeutic products are continually being made available. Only recently has substantial progress been made in the turn from the older "messy" preparations to more modern and agreeable creams and lotions. There is a substantial and recurring need for carefully controlled and diligent clinical evaluation of new preparations that may lead to improved dermatologic therapy. The patient is more likely to apply the preparation as directed if he is not embarrassed because of its color, odor or messiness. Many antiseborrheic preparations contain sulfur in one form or another, and consequently have an objectionable odor.

It is the purpose of this report to present the results of clinical studies of three new preparations which appear to be of sufficient therapeutic value to warrant further clinical evaluation.

Capsebon®

Many patients who seek dermatologic therapy have dandruff, excessive oiliness, pruritus

*Department of Dermatology, University of Alabama Medical Center, Medical College of Alabama, Birmingham, Alabama.

ROBERT A. LEWIS

BILLY L. FARMER

LAMAR S. OSMENT

RAY O. NOOJIN

or other manifestations of seborrheic dermatitis of the scalp. This condition may be controlled with appropriate local therapy, but it commonly recurs whenever treatment is discontinued. Heretofore, the most efficient preparations for this purpose have been somewhat unacceptable cosmetically because they were messy, had an objectionable odor or were otherwise disagreeable.

Recently, a metallic compound containing selenium sulfide was introduced as a shampoo, and it was found to be rather consistently effective as an antiseborrheic agent. Although its use has become widespread, it has caused such complications as diffuse loss of hair,[1] conjunctivitis,[2] and an increased oiliness of the scalp.

Capsebon, a new therapeutic shampoo, has been introduced more recently. This preparation contains 1 per cent of cadmium sulfide, a hair conditioner and a scenting agent in a detergent base. Rather extensive clinical studies and animal experiments have indicated that it does not cause any toxic reaction.[4-9] Adverse effects from the percutaneous absorption of cadmium compounds apparently have not been reported.[10] Capsebon apparently does not stain the hair or skin, and it does not irritate the epidermis or conjunctiva.

In a period of 24 months, we have used this preparation in 300 cases of seborrheic dermatitis of the scalp. Acne vulgaris also was present in 52 (17.3 per cent) of these cases. The treatment was carried out by the patients in the following manner, according to our directions. The scalp was shampooed two to seven times a week, depending on the severity of the involvement. The scalp was moistened with water, and a sufficient quantity of Capsebon was added to make an adequate lather. Approximately two teaspoonfuls of the preparation were necessary. After the application of the Capsebon, the scalp was massaged until an adequate lather developed. The lather was allowed to remain on the scalp for at least five minutes. The scalp then was rinsed thoroughly.

The treatment produced improvement in 242 (80.7 per cent) of the 300 cases. The term improvement designates: (1) objective evidence of a decrease in the oiliness, scaling or erythema and (2) subjective evidence of a decrease in the oiliness, scaling, pruritus or loss of hair. The original condition usually recurred when treatment was discontinued. In 50 (16.7 per cent) of the cases, the treatment did not produce any change in the condition. In eight (2.7 per cent) of the cases, the involvement of the scalp appeared to be worse after the treatment than it had been previously.

In all of the 300 cases, tincture of green soap was used as a shampoo and as a control either before or after Capsebon was used. Most of the patients said that they preferred the Capsebon because it was not as drying and made their hair softer. None of the patients who were improved by the use of this preparation objected to its use. After the hair was shampooed with this preparation, it appeared to be adequately cleansed and soft, and it did not have an unpleasant odor. The ready acceptance by most of the women patients was rather surprising, particularly in view of the fastidious care usually given the female coiffure. Most of the patients found that the preparation was cosmetically acceptable, and said

that it reduced the excessive oiliness. If the scalp was sufficiently rinsed after application of the shampoo, increased oiliness, loss of hair and staining of the hair were not noted. The treatment did not produce any toxic or allergic reaction, although at least 25 of the patients were known to have used the preparation regularly for 12 months or more.

The results which we have obtained with this preparation compare favorably with those reported by Mullins and Barnett[11] and other physicians.[10] Although Capsebon does not produce a permanent cure, it does appear to be one of the better antiseborrheic agents. The effectiveness and the cosmetic acceptability of this preparation would appear to warrant its further use.

Fostex®

To be effective as a local application in the treatment of seborrheic conditions, a drug should possess specific antiseborrheic, bacteriostatic and keratolytic properties. It also should have a low index of sensitivity and irritability.

Fostex is a combination of SEBULYTIC®, 2 per cent of salicylic acid, 2 per cent of micropulverized sulfur and 1 per cent of hexachlorophene. It is supplied in the form of a solid cake or a cream. The local use of each of the ingredients of this preparation has been shown to improve the seborrheic state or to exert a bacteriostatic effect.

Sebulytic is a combination of three anionic surfactants, namely, sodium lauryl sulfoacetate, sodium alkyl aryl polyether sulfonate and sodium dioctyl sulfosuccinate, which are of the soapless-cleanser and wetting-agent type. These agents apparently exert their cleansing, wetting and penetrating action by reducing the interfacial surface tension between molecules.[12] The most powerful of the anionic surfactants probably are the esters of sodium sulfosuccinic acid.[12] It has been demonstrated that sodium lauryl sulfoacetate does not cause any systemic reaction.[13] This agent also has been found to have good cleansing power, some antibacterial action, and a low order of allergenic action or irritability.[14] Anionic wetting agents as a group have been found to have an antiseborrheic and keratolytic effect.[15]

The salicylic acid has been added to enhance the keratolytic and bacteriostatic action of the Sebulytic. Salicylic acid is often used in an appropriate concentration for its keratolytic action in the treatment of acne vulgaris, seborrheic dermatitis, tinea and other types of dermatosis.[12,16] It also has some bacteriostatic action.[16,17]

The micropulverized sulfur has been added because of its proved usefulness in the treatment of acne and seborrheic conditions.[18,19] It is known that a combination of sulfur and salicylic acid produces a stronger keratolytic action than either of these agents does when used alone.[20]

Hexachlorophene has been used because of its antibacterial properties. Several investigators[21-23] have demonstrated that this agent has a powerful bacteriostatic action. Moreover, Fahlberg, Swan and Seastone[24] demonstrated that hexachlorophene could be recovered from the skin two days after a 1 per cent solution of this drug in liquid soap had been applied for six minutes on three consecutive days.

We have used Fostex in 215 cases of acne vulgaris and in 118 cases of seborrhea capitis. Either the cream or the cake was used in these cases. One of these preparations was applied twice a day. After the skin had been wetted, the cream was applied, made into a lather, and massaged into the skin for approximately five minutes before it was removed by rinsing. The cake was used as a soapless cleanser and was massaged into the involved areas for five minutes.

In these 215 cases, the condition had previously failed to respond after four weeks of routine acne therapy including a restricted diet, office removal of comedones, ultraviolet therapy, local application of SULFORCIN® lotion, and meticulous cleansing of the face and scalp with soap and water.

Improvement occurred in 161 (74.8 per cent) of the 215 cases. In these 161 cases, there was a decrease in the oiliness and in the number of comedones, papules and pustules. The condition remained unchanged in 49 cases. In five cases, the condition appeared to be worse after the treatment than it had been

previously. Thirty-one of the patients complained of an excessive drying effect, which could be alleviated by applying the treatment less frequently. The odor of the preparation, like that of other preparations of sulfur, was generally deprecated. No serious side effects or evidence of sensitization was observed in any of these cases.

We also have used Fostex cream in 118 cases of seborrhea capitis. The cream was used to shampoo the scalp two to seven times a week, depending on the severity of the condition. After the hair had been wetted, the cream was applied, made into a lather, and massaged into the scalp for approximately five minutes before it was removed by rinsing. Improvement occurred in 95 of the 118 cases, but no change in the condition was observed in 18 cases. In five cases, the condition apparently was aggravated by the treatment. In the cases in which improvement occurred, a decrease in the scaliness and oiliness was observed after the treatment had been continued for two or three weeks. Pruritus usually disappeared by the end of this period. Some of the patients who objected to the use of the Fostex cream complained that it took the natural curl out of their hair, that it was too drying, that it was irritating, or that it had an objectionable odor. The only objectionable sign noted was the occasional occurrence of excessive dryness, which was controlled by applying the cream less frequently.

Our experience with Fostex in the treatment of acne vulgaris and seborrhea capitis has been similar to that reported by other authors.[25,26]

Acnaveen®

The successful treatment of acne vulgaris continues to require the local application of an antiseborrheic, desquamating and antibacterial agent. Acnaveen, a preparation containing colloidal oatmeal, kaolin, 3 per cent of sulfur U.S.P. and 0.5 per cent of hexachlorophene, recently has been made available for use in the treatment of acne vulgaris and seborrheic dermatitis. When colloidal oatmeal is applied locally, it possesses highly absorptive properties for scales, dirt, sebum and cellular debris.[27] Its subsequent removal with soap and water results in a superior cleansing effect. The application of sulfur affords a keratolytic, desquamating and drying effect known to be beneficial in the treatment of acne vulgaris.[18,19] Hexachlorophene, a safe antibacterial agent, has been added for its effectiveness against staphylococci.[21-23]

We have used Acnaveen in 120 cases of acne vulgaris in a period of 20 months. In all of these cases, the usual therapeutic regimen, including dietary restriction, office removal of comedones, ultraviolet therapy, local application of Sulforcin lotion, and thorough cleansing of the face and scalp with soap and water, had been used for four weeks but had not produced a satisfactory response. The Acnaveen then was used in addition to the usual therapeutic regimen.

One tablespoonful of Acnaveen powder was mixed with one tablespoonful of water in a teacup. The resulting mixture was applied as a thick coating to the face, which was subsequently massaged. The coating was allowed to dry for 15 minutes, and it then was removed with a washcloth and water. The Acnaveen was applied once or twice a day, depending on the severity of the eruption.

Improvement occurred in 66.7 per cent of the cases, but no change was observed in 30 per cent of the cases. The condition apparently was aggravated in 3.3 per cent of the cases. The term improvement designates objective evidence of a decrease in the oiliness and in the number of comedones and pustules. Although the Acnaveen frequently was effective, some patients complained that it was too messy, that its application was too time-consuming, or that it was difficult to remove. No evidence of sensitization was noted. Apparently, one of the beneficial attributes of this preparation is that it can be removed only after much scrubbing.

Since appropriate local therapy continues to be important in cases of acne vulgaris, promising new agents of this type deserve adequate clinical trial.

Capsebon was supplied through the courtesy of Dr. P. A. Boyer, Jr., of the Pitman-Moore Company of Indianapolis, Indiana; Fostex cream and cake were supplied through the courtesy of Charles A. Oclassen of the

Westwood Pharmaceuticals of Buffalo, New York, and Acnaveen was supplied through the courtesy of Sidney Musher of the Aveeno Corporation of New York.

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MEETINGS *and Postgraduate Courses*

Southern Thoracic Surgical Association, Miami Beach: Annual meeting, November 29-30, at the Deauville Hotel. For further information, write to: Dr. Hawley H. Seiler, Secretary, Southern Thoracic Surgical Association, 517 Bayshore Boulevard, Tampa 6.

University of Minnesota, Minneapolis: Courses for 1959 to be given at the Center for Continuation Study:

Otolaryngology, January 5-7 and May 27-29
Newer drugs, January 15-17
Surgery, January 22-24
Cardiovascular diseases, February 23-25
Pediatrics, March 2-4
Trauma, March 14
Internal medicine, March 16-18
Water and electrolyte balance, March 30-April 3
Emergency surgery, April 2-4
Radiology, April 6-8
Allergy, April 16-18
Introduction to electrocardiography, May 11-15
Proctology, May 18-22
Gynecology, June 15-17

For further information, write to: Director, Department of Continuation Medical Education, 1342 Mayo Memorial Building, University of Minnesota, Minneapolis 14.

University of Texas M. D. Anderson Hospital and Tumor Institute, Houston: Thirteenth annual symposium on fundamental cancer research, February 26-28. For further information, write to: Felix L. Haas, General Chairman, Department of Biology, M. D. Anderson Hospital, Houston 25.

Editorials

Postgraduate Medicine

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Contributing Editor:
MORRIS FISHBEIN, M.D.

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SYLVIA COVET

THE CHANGING CLIMATE OF SURGICAL RESIDENCIES

SURGICAL residency training could be obtained in a limited number of teaching centers in this country prior to World War II, but its widespread availability and general acceptance date from about 1946. At that time Veterans Administration Hospitals entered the field under the deans' committee plan of affiliation with the medical schools. Simultaneously, residency programs were developed in certain military hospitals and in many civilian-staffed institutions which previously had not been regarded as teaching hospitals. Unique circumstances at the war's end made this unprecedented expansion of residency training both possible and desirable. The contrast found only 12 years later is so striking as to deserve attention and, very likely, a re-evaluation of our residency programs.

At the close of World War II, there were great numbers of men whose surgical training had been interrupted or deferred. The savings they had accrued during their time on active duty and the benefits of the GI bill enabled them to devote several years to the specialized training they desired. Moreover, they had no firm roots and were willing to go wherever the opportunity for good surgical training existed. This mature group of men, who knew exactly what they wanted, set a high standard of performance for the residents who were to follow them. When they had completed their training, they encountered favorable circumstances for finding desirable areas for practice. There existed a widespread demand for specialists, and the Hill-Burton Act had stimulated the construction of modern hospitals with good surgical facilities. Many of these institutions were anxious to secure well-trained specialists. The young surgeons who had manned aid stations or remote island dispensaries a few years earlier were ready to take advantage of these openings. They had economic and spiritual independence, which allowed them to choose a location that suited them, and today they are well established.

A dozen years later, candidates for surgical residency positions emerge from a different environment and, at the close of training, begin practice in a greatly changed world. Today's candidate is four or five years younger than his 1946 counterpart and is considerably less mature. Some have completed their military service, but most of them must look for-

ward to two years of duty. (Unfortunately, some apply for residency not because of an unquenchable desire to be surgeons but with the hope of deferring or, perhaps by some miraculous chance, evading those years of military service.) The GI benefits with which earlier residents were endowed have now been exhausted. There is no evidence of race suicide, and the residents of 1958, with less capital savings to see them through, appear to have even larger families than did those of 1948. Thus, economic factors seriously limit the number who can afford the long years of residency training. Moreover, salary scales and fringe benefits, such as family housing, play a conspicuous role in selecting a hospital. (Provision of loan funds to aid some residents throughout their training period is greatly needed. What an opportunity this presents for individuals or professional organizations such as local surgical societies.) The stampede into the specialties reached its height some years ago, and today a larger proportion of medical graduates are being drawn into general practice. This is another factor which has reduced the demand for the available surgical residency positions.

For all of these reasons, there are a great many more residency positions available today than there are qualified applicants to fill them. In this buyer's market, directors of residency programs find themselves in the strange position of being interviewed by candidates who seek assurance of short hours and many operations. It is obvious that the number of residency positions should be curtailed, but everyone believes this should begin in some hospital other than one's own. In time, the law of supply and demand will assert itself, and the hospitals which offer the best training programs will survive. Meanwhile, the challenge of competition should spur all to improve the quality of their teaching.

Not only are the residents of today a somewhat different breed than those of a decade ago, but their attitude toward practice and the conditions thereof are changed. Many communities are saturated with specialists in certain branches of surgery, but, curiously, this bears no relation whatever to the proportion of applicants for the various programs. Many large centers, certainly those adjacent to a medical school, are oversupplied with young general and thoracic surgeons; however, although there is a considerable demand for orthopedists and otolaryngologists, not too many enter these residency programs. Nevertheless, there are still cities with good hospital facilities where a well-trained general surgeon can reasonably expect to establish himself within a few years if he is adventurous enough to seek out such opportunities and willing to make himself available and to work hard.

Too many of our young men believe the world owes them an immediate living, and they shun the risks involved in entering these smaller communities. Ironically, they continue timorously to congregate in the metropolitan areas, where actually the "starvation period" for surgeons may be longer. I do not for a moment suggest that young surgeons deserve a "red carpet" reception in whatever community they select, but I do believe they should be given a fair opportunity to prove their worth. Moreover, it is no credit to the profession that some communities are closed to an honest and well-trained surgeon unless he will compromise with his conscience. The price of his acceptance is to agree to the unethical practice of fee-splitting or to the exploitation of his superior training as "ghost assistant" to some older man who should not pretend to do surgery. All concerned with the training of surgeons and with the good name of American surgery should use their influence to eliminate these practices. The young men are its victims. They must comply or go elsewhere.

JOHN PAUL NORTH
Chief, Surgical Service
Veterans Administration Hospital, Dallas

AUTOMATION IN MEDICINE

In the Spring-Summer issue of *Outlook*, published quarterly by the University of Chicago Council on Medical and Biological Research, attention was called to various laboratory devices now employed for saving labor by substituting mechanical, electric or hydraulic power for human muscle or for carrying out

processes under conditions in which a human worker could not survive. Also used for automatically processing data are rapid-computing machines which repeat tirelessly and accurately various monotonous procedures. Another type of equipment is that in which an automatic self-control functions as the result of applying the principle of feedback.

The publication notes that hospitals and medical research institutions have lagged far behind industry and the military in utilizing automatic devices. For example, an automatic cell counter takes the place of the usual process of counting blood cells. The automatic red cell counter will count a sample of 50,000 cells in about 15 seconds and will do a triplicate count in little more than a minute. Such cell counts are more reliable than those done with the usual microscope. Experiments are under way to expand the use of this equipment so that white blood cells also may be counted.

Another device is the chemostat, which permits continuous culture of bacteria at a predetermined level of growth. With this device the effects of various substances on the growth of bacteria also may be detected. The Univac is used to analyze large masses of numerical data relating to different variables concerned in physiology.

An automatic blood chemistry machine can perform 20 analyses an hour for blood sugar and for blood urea nitrogen. Another device is an automatic liquid scintillation counter which measures radioactive content. A hot cave protects an investigator while he manipulates substances with intense radiation. The walls of the cave are 15 in. thick and the window through which the experimenter works contains a solution of lead bromide. With the help of a high-speed computer and a magnetic-core memory, a pulse-height analyzer can perform in a matter of minutes measurements involving 256 different energies. This device is particularly important in identifying simple isotopes. For some years IBM tabulators have been used in the business offices of the University of Chicago Clinics for greater accuracy and efficiency in auditing.

These are just a few examples of the trends in the adaptation of new technics to medical research and clinical activities. The rate of discoveries and their adaptation is so rapid that the physician who was graduated 20 years ago is amazed at the revolution that has occurred in the processes employed in clinical investigation.

MORRIS FISHBEIN

THE LONG-TIME TRENDS IN ILLNESS

In studies of business, large industries nowadays avail themselves of the services of economists who are concerned with cycles and trends. In medicine, the epidemiologists and the statisticians are chiefly involved in such studies which are commonly based on records of births, deaths and marriages. More recently, the records of nonfatal illness are being studied to note the presence and spread of infectious diseases and to assist in the suppression of epidemics.

Historically, Thomas Cromwell (1485-1540), vicar-general under Henry VIII of England, is credited with being the first to set up in any country a system of registration of births, deaths and marriages. In a recent study[1] of "Long-Time Trends in Illness and Medical Care," Collins of the U. S. Public Health Service credits William Farr of England with establishing the principles for estimating the prevalence of illness in any locality; these were based on some ratio of illnesses to deaths. The principle was that the percentage of the population constantly sick equals twice the annual death rate per one hundred persons. Extensive studies have been made by the Metropolitan Life Insurance Company, the U. S. Children's Bureau and, particularly, by Dr. Edgar Sydenstricker of the U. S. Public Health Service.

Due to discoveries in such fields as anesthesia, x-ray and bacteriology, and with the development of antibiotics, the important causes of death are no longer the acute infectious diseases nor diseases of young adults but noninfectious, chronic diseases of older ages. Of these, the cardiovascular-renal group causes about 54 per cent of deaths in the United States. Some acute infectious diseases are

still serious causes of crippling and death. In July 1956, Congress passed a bill providing for a continuous survey of illness in representative sample areas of the United States. No doubt, important information will come from the various surveys as the results become available.

In Public Health Monograph No. 48 just made available by the U. S. Public Health Service,[1] all important surveys of recent years are analyzed, and studies are reported on age and sex variations in disease, hospital surgical and nonsurgical cases, seasonal variations in illness, trends among civilians and in the armed forces, life expectancy, mental diseases, mortality and illness in urban and rural areas, and similar subjects. Special sections are concerned with influenza and pneumonia and with notifiable diseases.

From the studies that have been made, some important facts become apparent. The rates of first admissions to mental hospitals for the major psychoses, psychoneuroses and mental disorders without psychoses are highest in patients around 40 years of age and decline thereafter. The first admission rates for epileptics and mental defectives are highest in patients from 10 to 19 years of age.

The peak prevalence rate for tuberculosis in long-term hospitals occurs in women in their early twenties and in men from 50 to 60 years of age.

The proportion of total births in the United States occurring in hospitals increased from 37 per cent in 1935 to 94 per cent in 1955.

Women industrial workers show consistently higher illness rates than men. The life expectancies of women have been consistently higher than those of men. In the United States, the life expectancy rate has risen from about 35 years in 1780 to about 68 years for men and 72 years for women in 1955. Similar rates prevail in England, France and the Netherlands, but the excess of life expectancy in women over men is least in the Netherlands, next lowest in England and approximately the same in the United States and in France.

So rapid is the advance of medicine nowadays that studies have to be made continuously, as has been proposed by the Congress, in order to understand the changes necessitated by changing conditions. At present, hospitals and sanatoriums for tuberculosis patients are being closed in great numbers; conceivably this is a trend likely to continue as better drugs and better systems for their use are developed. The development of new drugs affecting the brain is permitting the discharge of considerable numbers of persons from institutions for the mentally disturbed. As drugs are perfected and understanding becomes greater, this trend too should continue. The medical care and hospitalization of veterans and the care of persons in the armed forces have placed great demands on medical services; these demands should decrease with time unless political developments bring greater threats to security, necessitating the involvement of greater numbers of persons in defense. Actual wars, with the development of new weapons of destruction, are likely to place still greater demands on medical services than the control of disease.

MORRIS FISHBEIN

REFERENCE

1. Collins, S. D.: Long-Time Trends in Illness and Medical Care. Public Health Monograph No. 48, U. S. Department of Health, Education and Welfare, Public Health Service. Washington, D.C., Government Printing Office, 1957.

OLD AGE AND RETIREMENT

The Department of Social Medicine in the University of Birmingham in England has been concerned with the lack of scientific data on the medical condition of persons in the seventh decade of life. Obviously, the physical capacity of men more than 70 years old is an important factor in relation to their employment. Therefore, the Department undertook to examine a group of representative men aged 60 to 69, using the standards required for life insurance purposes. In the study,[1] the cooperation of 11 general practitioners in Birmingham was enlisted. In the appropriate age group, there were 1,243 men of whom 1,062 were examined. The physicians attempted to see all persons either in their own homes or else in the doctor's office. The medical exami-

nations included a chest roentgenogram and, when necessary, appropriate investigation by a specialist. Coronary disease was made the subject of a separate inquiry. From these studies some important data have been assembled. Indeed, enough information was collected to indicate the significance of the general practitioner's contribution to social medical research.

In the seventh decade of life, chronic bronchitis was both the most common disease and the one associated most frequently with disability. Studies were made to determine whether or not smoking bore any relationship to chronic bronchitis. The information collected indicated that smoking did not greatly increase the risk of chronic bronchitis for men in professional and related occupations, whereas the risk was trebled for men in unskilled occupations. The investigators were not able to determine just why this relationship should prevail. However, in other infectious diseases affecting the respiratory tract, as, for example, pneumonia, the incidence is also more frequent among persons in less favorable social circumstances. Arterial hypertension was not related to physical and mental demands of occupation. A diagnosis of coronary disease was confirmed in 89 cases.

The men studied were divided into five social classes, beginning with professional occupations and extending into the fifth class of unskilled occupations. From class 1 to class 5 the proportion of men with disease increased regularly. The incidence of peptic ulcer increased consistently from class 1 to class 5, but the association was different in duodenal ulcer. Among the chief difficulties in relation to employing persons of advanced years were defective hearing and defective vision. The proportion of men considered unfit for employment was approximately 1 in 10 in the whole group, one in seven in persons more than 65, and one in four in persons around 70 years of age. The proportion of men over retirement age and unfit for employment was related sharply to their social class. Among persons in professional and related occupations, 1 in 10 was considered unfit for employment, but among persons in some skilled and unskilled occupations the number was one in five.

The Birmingham physicians, Brown, McKeown and Whitfield, are convinced that if an advancement of retirement age were considered obvious for other reasons, there would appear to be no medical grounds to prohibit it.

MORRIS FISHBEIN

REFERENCE

1. Brown, R. G., McKeown, T. and Whitfield, A. G. W.: Observations on the medical condition of men in the seventh decade. Brit. M. J. 1:555-562 (March 8) 1958.

THE "RUNNING START" IN MEDICAL WRITING

Many years ago when I was assistant to the editor of the *Journal of the American Medical Association* (1913 to 1924) my preceptor, the famous Ludvig Hektoen, occasionally used to send me post cards on which he had written his abominations in scientific writing. He numbered the cards consecutively, and I still treasure them these many years. Recently, while reading an issue of a widely circulated medical journal, I observed frequent instances of what has come to be my pet abomination. I call it the "running start." Here are a few examples:

"It is generally agreed that . . ." *By whom?*

"In spite of the fact that . . ." *Why not "although"?*

"It is probable that . . ." *Why not "probably"?*

"I would like to say that . . ." *Who is stopping him?*

"I shall discuss . . ." *Why threaten?*

"It is my intention to present . . ." *So go ahead!*

"It should be pointed out . . ." *So point out!*

"There would seem to be . . ." *So, scientifically, is there?*

All these were in one issue. Psychologically the "running start" is an indication of doubt by the writer or speaker of what he is going to say or whether or not it is really worth saying. We may as well accept his own valuation.

MORRIS FISHBEIN

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SUPPLIED: Prescription only. *Tablets,* 10 mg., 25 mg., and 100 mg., bottles of 100. *Syrup,* pint bottles. *Parenteral Solution,* 10 cc. multiple-dose vials.

1. Burrell, Z. L., et al.: Am. J. Cardiol. *1*:624 (May) 1958. 2. Feinberg, A. R., et al.: J. Allergy *29*:358 (July) 1958. 3. Eisenberg, B. D.: Clin. Med. *5*:897 (July) 1958. 4. Robinson, H. M., Jr., et al.: South. M. J. *50*:1285 (Oct.) 1957. 5. Strub, I. H.: Personal communication. 6. Schuller, B.: Gaz. des Hôpitaux No. *10*:391 (Apr. 10) 1957.

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PRODUCER: General Electric Co., X-Ray Department, Milwaukee.

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(Continued on page 118)

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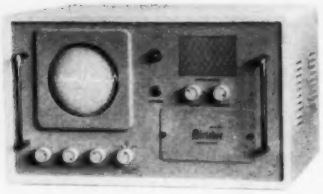

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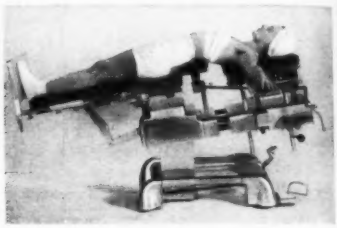

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PRODUCER: Physicians' Record Co., Chicago.

(Continued on page A-120)

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(Continued on page A-122)

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Doshay, L.J., and Constable, K.: Treatment of Paralysis Agitans with Orphenadrine (Disipal) Hydrochloride: Results in One Hundred Seventy-Six Cases, J.A.M.A. *163*:1352 (Apr. 13) 1957.

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Finch, J.W.: Clinical Trial of Orphenadrine (Disipal) in Skeletal Muscle Disorders. Scientific Exhibit at Mississippi Valley Medical Society Meeting, St. Louis, Missouri, Sept. 3-5, 1957.

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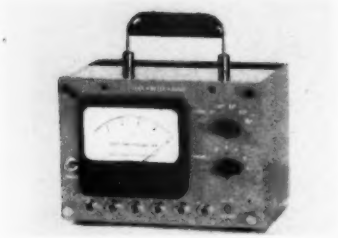

• YSI THERMISTEMP THERMOMETER (Model 46 TUC)

DESCRIPTION: Covering the range from 0 to 50° C. in five overlapping ranges, each 11° C. wide, this multichannel, multirange thermometer has an absolute accuracy of ± 0.15 C. and a readability of 0.05 C. over its entire range. Five separate meter shunt circuits assure the linear presentation of the thermistor response. Powered with a mercury battery, the instrument is equipped with a recorder jack which permits any potentiometer recorder with a span of 100 mv. or less to record temperatures.
PRODUCER: Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio.

• CAPSEBON® SHAMPOO

PURPOSE: To control seborrheic dermatitis.
COMPOSITION: 1 per cent cadmium sulfide suspension in a shampoo base.
PRODUCER: Pitman-Moore Co., Indianapolis.

• VESPRIN® EMULSION (New Dosage Form)

DESCRIPTION: A bland, orally administered, vanilla-flavored stable liquid, this new form of Vesprin is particularly suitable for problem patients who refuse the drug in tablet form or who secrete tablet medication. It also may be used by pediatric and adult patients who have difficulty in taking tablets and by geriatric patients who do not properly absorb medication from the gastrointestinal tract. Each cubic centimeter contains the equivalent of 10 mg. trifluprom azine hydrochloride.
HOW SUPPLIED: Dropper bottles of 30 cc. and bottles of 120 cc.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

• HEPARIN SODIUM (New Package Forms)

DESCRIPTION: This anticoagulant is now available in 1 cc. ABBOJECT® disposable syringes and 5 cc. multiple-dose vials, each form containing 20,000 U.S.P. units per cubic centimeter. Each intramuscular or deep subcutaneous injection from the Abboject syringe is effective for about 12 hours. Excess air should be extruded before injection. When using the multiple-dose vials, initial intramuscular or deep subcutaneous injections of 10,000 to 20,000 units may be followed by 10,000 units every eight hours or 12,000 units every 12 hours, depending on clotting time. For intravenous administration, dilute concentrated solution of heparin with sterile solutions of isotonic sodium chloride or 5 per cent dextrose or Ringer's solution to provide 20,000 to 50,000 units per liter. This allows continuous intravenous infusion at the rate of about 40,000 units every 24 hours. The usual precautions pertaining to the administration of heparin should be observed.
PRODUCER: Abbott Laboratories, North Chicago.

• MICRO-FILTER

DESCRIPTION: Designed for use with the ISOLETTE® infant incubator, this air filter removes contaminants, including staphylococci, from hospital nursery air and thus helps minimize the danger of air-borne infections. When equipped with the Micro-Filter, the Isolette provides complete isolation even when not connected to an outside air source. The unit consists of a polished cast-aluminum filter body, plastic cover, oxygen input nipples, fasteners adapted to an Isolette incubator, and 12 Micro-Filter pads (approximately one year's supply).
PRODUCER: Air-Shields, Inc., Hatboro, Pa.

(Continued on page A-124)

NEW RELEASE!

MORE COMPLETE CONTROL IN ANXIETY COMPLICATED

STEROID-RESPONSIVE DISEASES

NEW STEROTRIL

METICORTEN® plus TRILAFON®

SYNCHRONIZES CORTICOID TRANQUILIZER BENEFITS

- enhances "Meti" steroid response by allaying the stress overlay
- frequently reduces steroid dosage requirements and thus lessens likelihood of side effects
- forestalls anxiety-triggered flare-ups and relapses
- simplifies dosage schedules in combined therapy
- renders patients more calm and cooperative

in rheumatoid arthritis and other rheumatic disorders, allergic dermatoses, bronchial asthma and other serious respiratory allergies, drug reactions, collagen diseases

and whenever a corticoid-tranquilizer combination is indicated

STEROTRIL* Tablets, 2.5 mg. prednisone and 2 mg. perphenazine; bottles of 30 and 100.

Meti,® brand of corticosteroids.

Schering

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

*T.M. ST-J-198

• NO. 8 M•P SURGICAL LIGHT

DESCRIPTION: Designed for office, clinic and industrial examining room use, this light has concentric-cone light configuration to produce a constant and unchanging light pattern over a 2 to 5 ft. focal range and to minimize glare and shadow. It gives a color temperature as close to average daylight as is possible. Measurement of the center of the spot indicates 2000 foot-candles maximum to 1000 foot-candles in a field size of 6 to 8 in., measured 42 to 35 in. from lens to subject. The light is available as a floor lamp or for wall or ceiling mounting. In the floor model the lamphead moves 360 degrees around a vertical upright and swivels in every plane, so that it can be beamed to the field from any angle. The lamphead is interchangeable between models.
PRODUCER: Wilmot Castle Co., Rochester, N.Y.

• ACTIDIL® TABLETS AND SYRUP

PURPOSE: Antihistaminic action.
COMPOSITION: Triprolidine hydrochloride: 2.5 mg. in each tablet; 1.25 mg. in each 5 cc. syrup.
INDICATIONS FOR USE: Hay fever, pollinosis, drug sensitivity, pruritus, allergic dermatitis and vasomotor rhinitis.
DOSAGE AND ADMINISTRATION: Adults, 1 tablet or 2 teaspoonfuls syrup; children more than two years of age, ½ tablet or 1 teaspoonful syrup; infants, ¼ tablet or ½ teaspoonful syrup. Doses should be administered two or three times daily.
HOW SUPPLIED: Tablets in bottles of 100; syrup in 1 pt. bottles.
PRODUCER: Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N.Y.

(Continued on page A-126)

When POSTOPERATIVE OOZING Persists...

Efficacy of Antihemophilic Plasma in controlling the postoperative oozing that often occurs when patients have been massively transfused with banked blood has been reported by Howland.* He describes routine use of this specially processed plasma when oozing persists after closure of the wound. Fibrinolysis, he found, "usually responds dramatically" to its administration. Why this hemostatic efficiency? Because Antihemophilic Plasma is *fresh* plasma that has been rapidly processed to retain the labile clotting factors which are rapidly lost in banked blood. Hyland Antihemophilic Plasma (Irradiated, Dried) requires no grouping, typing or crossmatching. Just reconstitute with accompanying diluent and it is ready to administer.

Five-year dating. Available in 3 sizes: 50 cc. with built-in filter for syringe administration; 100 cc. and 250 cc., each with administration set.

*Howland, W. S.: Cardiovascular and Clotting Disturbances during Massive Blood Replacement, Anesthesiology 19 (2): 140-152 (March-April, 1958).

Hyland Laboratories, 4501 Colorado Blvd., Los Angeles 39, Calif. • 160 Lockwood Ave., Yonkers, N.Y.

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HYLAND

ASTHMA CONTROLLED WITH STEROTRIL

L. B., 29, executive secretary to steel mill president; bronchial asthma of 4 years' duration, acute attack with severe anxiety related to breathing difficulty; typical wheezing and coughing; placed on STEROTRIL; markedly improved on first day, totally asymptomatic and able to return to work on third day. Continued on STEROTRIL maintenance regimen.

ASTHMA AND ALL SEVERE RESPIRATORY ALLERGIES AGGRAVATED BY ANXIETY RESPOND VERY WELL TO **STEROTRIL**

SCHERING

STEROTRIL® Tablets, 2.5 mg. METICORTEN® (prednisone) and 2 mg. TRILAFON® (perphenazine); bottles of 30 and 100.

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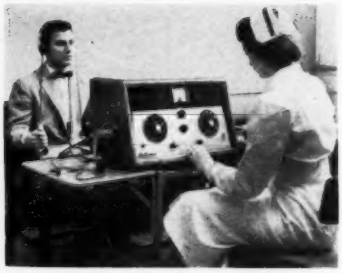


• DIAGNOSTIC AUDIOMETER
(Model 14-A)

DESCRIPTION: Featuring a transistorized speech circuit and simplified loudness-balance control, this unit accurately performs alternate loudness-balance binaural recruitment tests. The range of attenuation is from –10 to 100 decibels, and interpolation can be made in one decibel step. With a transistorized speech circuit to reduce hum noise and microphonics, it is possible to conduct 17 different types of speech and pure-tone hearing tests. Accessories include double air-conduction receivers, bone-conduction receiver, microphone, monitor phone, patient's button signal and switch, dust cover, instruction manual and audiogram blanks.
PRODUCER: Beltone Hearing Aid Co., Chicago.

• NEOSPORIN® VAGINAL SUPPOSITORIES

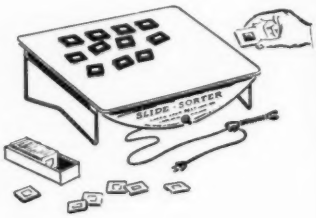
PURPOSE: Bactericidal and trichomonacidal action and to restore normal vaginal pH.
COMPOSITION: Each wedge-shaped suppository contains:

AEROSPORIN® (polymyxin B sulfate)	20,000 units
Neomycin sulfate	5 mg.
Acetarsone	250 mg.
Beta-lactose	q.s. (approximately 1 gm.)

These agents are combined in a water-soluble base containing a wetting agent.
INDICATIONS FOR USE: Vaginitis, cervicitis, trichomoniasis, presurgical and postsurgical treatment, infertility due to cervicitis, and malodorous discharge due to infection.
DOSAGE AND ADMINISTRATION: The usual dosage is 1 suppository inserted high in the vagina once or twice daily for 6 to 10 days or as required.
HOW SUPPLIED: Boxes of 12.
PRODUCER: Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N.Y.

• GRADUMET® TRAL®
(New Dosage Form)

PURPOSE: To provide anticholinergic action.
COMPOSITION: Each tablet contains 50 mg. hexocyclium methyl sulfate. Also available with 30 mg. phenobarbital.
DESCRIPTION: Consisting of physiologically inert plastic with hundreds of interstitial passages impregnated with the medication, this tablet provides gradual, metered relief over a 12 hour period.
INDICATIONS FOR USE: Peptic ulcer, gastrointestinal disorders associated with hyperacidity and hypermotility, and certain spastic conditions of the intestinal tract.
DOSAGE AND ADMINISTRATION: Initial dosage, 1 tablet twice daily before lunch and at bedtime or before breakfast and dinner.
HOW SUPPLIED: Bottles of 50 and 500.
PRODUCER: Abbott Laboratories, North Chicago.



• SLIDE-SORTER

DESCRIPTION: Photographic slides are quickly and easily sorted and arranged for screen projection with this unit, which consists of a smooth, unbreakable, translucent plastic work surface mounted on a baked-enamel wire stand. Light from a 40 W lamp assembly is reflected by a built-in aluminum reflector up through the work surface, providing a soft, evenly diffused light. Up to 40 slides may be examined at one time.
PRODUCER: The H. E. Geist Company, Cleveland.

• CLUSIVETS®
(New Dosage Form)

PURPOSE: Nutritional supplement.
COMPOSITION: Vitamins and essential minerals.
HOW SUPPLIED: Bottles of 100.
PRODUCER: Ayerst Laboratories, New York.

(Continued on page A-128)

the unique nitrofurans eliminate

problem pathogens

problem pathogen: Staphylococcus aureus

"The ability of this organism to adjust to its antibiotic environment is one of the major problems in medicine today."*

FURACIN CASE REPORT: STAPHYLOCOCCAL OSTEOMYELITIS

Severe compound fracture of right foot led to a large, open ulcerated wound on the sole, with tarsal bones exposed and necrotic. Despite extensive debridement, removal of necrotic bone and attempted closure with a pedicle flap, the wound failed to heal and developed considerable purulent drainage.

Culture of pus revealed Staphylococcus aureus, *resistant to all antibiotics tested,* but sensitive to FURACIN. Daily irrigation was instituted, employing 1 part of FURACIN Solution to 4 parts normal saline. Depths of the wound were reached with a long #20 needle on a 20 cc. syringe.

Purulent drainage decreased considerably within a few days, stopped completely after 2 weeks of irrigation with FURACIN Solution. The open space beneath the pedicle flap gradually filled with healthy granulation tissue, and 6 weeks after institution of FURACIN treatment, healing was complete.

In clinical use for more than 12 years and today the most widely prescribed single topical antibacterial, FURACIN—like other nitrofurans—remains effective against pathogens which have developed, or are prone to develop, resistance to antibiotics.

The NITROFURANS

Products of
Eaton Research

FURACIN® brand of nitrofurazone

Available as Soluble Dressing, Soluble Powder, or Solution. Also in Vaginal and Urethral Suppositories and in special formulations for eye, ear and nose.

*Koch, R., and Donnell, G.: California Med. 87:313, 1957.

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NEW YORK UNIVERSITY

Post-Graduate Medical School

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ARTHRITIS AND ALLIED RHEUMATIC DISORDERS
Full-time, November 10 through 14, 1958.

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Full-time, December 1 through 19, 1958.

For additional information:

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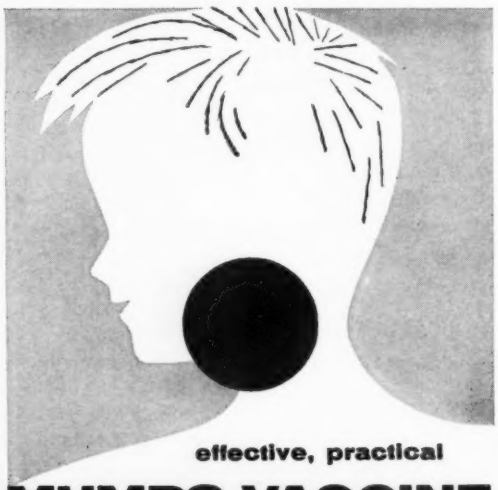
550 First Avenue New York 16, N. Y.



effective, practical

MUMPS VACCINE

A specific immunizing antigen (chick embryo origin) for prevention or modification of mumps in children and adults.

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LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY
PEARL RIVER, N. Y.

New for Your Armamentarium

• DISPOSABLE EXAMINING GLOVES

DESCRIPTION: Available in medium and large sizes, these gloves are made of strong vinyl plastic which conforms to the fingers, providing good tactile sensitivity. Each glove is powdered to facilitate slipping onto the hand, and is ready for immediate use. Since they are used only once, cross-contamination is avoided. The gloves are supplied in a specially designed dispenser box.
PRODUCER: Emergency Kit Corporation, New York.

• DUO-TRACE CARDIOSCOPE

DESCRIPTION: Designed for monitoring and comparing two physiologic signals, this instrument displays two traces on a 5 in., long-persistent screen. It has a frequency range to 2000 cycles per second, a continuously variable sweep rate from 7.5 to 100 mm. per second, and a sensitivity of 330 μv per centimeter. Base-line stability circuits restore the trace to the center of the screen approximately one second after it has been driven off scale. The instrument may be used for simultaneously observing electrocardiographic and electroencephalographic signals in monitoring anoxia during surgery. Other uses include monitoring in the recovery room and cardiac ward, cardiac catheterization and phonocardiography. The instrument weighs 35 lb. and operates from standard 115 V 50/60 cycle current; other input voltages for export are available on special order. Optional accessories include a preamplifier, which increases the sensitivity to 10 μv per centimeter, and a 5 ft. high steel cart on which to place the cardioscope during surgery. For permanent recording of signals, an output jack is provided for each channel to which standard electrocardiographic or other recording equipment may be attached.
PRODUCER: Levinthal Electronic Products, Inc., Palo Alto, Calif.

F THE URINALYSIS SHOWS INFECTION:

ew Pyridium Tri-Sulfa, for acute urinary tract infections, is the only ombination treatment which provides the therapeutic dose of analgesic yridium with only 1 tablet four times daily. Provides symptom relief less than 30 minutes plus broad nd efficient antibacterial action. **PYRIDIUM® TRI-SULFA**

(PHENYLAZO-TRISULFAPYRIMIDINE)

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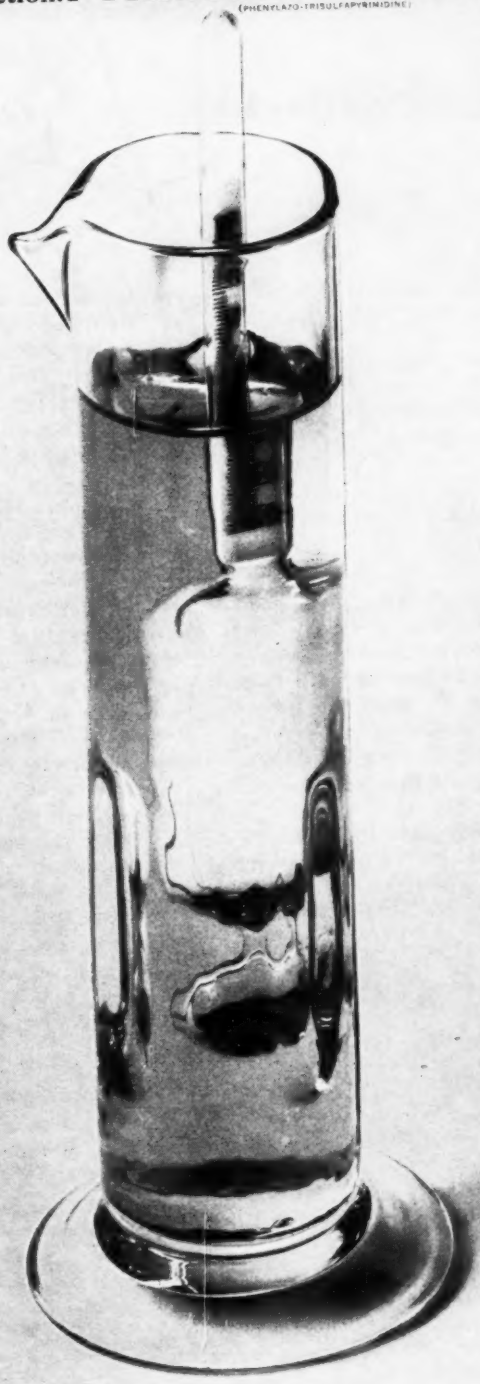

THE MEDICAL *Bookman*

► HEART DISEASE IN INFANCY AND CHILDHOOD

By John D. Keith, M.D., Assistant Professor of Pediatrics, Richard D. Rowe, M.B., Clinical Teacher, Department of Pediatrics, University of Toronto Faculty of Medicine, Toronto, Canada, and Peter Vlad, M.D., Instructor in Pediatrics, University of Buffalo School of Medicine, Buffalo. 877 pages, illustrated. 1958, The Macmillan Company, New York. $22.50.

In this extensive, well-written and amply illustrated book, the authors have covered in detail congenital and acquired heart disease in infancy and childhood. Drawing on their vast experience and on a thorough review of the work of others, they have written the most complete book on pediatric cardiology yet published. The bibliography is one of the largest yet assembled in one textbook.

The presentation of the diagnostic principles and methods used in the practice of cardiology is simple enough to be understood by the student, but comprehensive enough to provide a reference for the cardiologist and physiologist. The clear discussion of fundamentals in the chapters devoted to heart sounds, blood pressure and electrocardiography is invaluable to the student. However, the chapter on electrocardiography is a little disappointing in that there is more emphasis on the electrocardiographic patterns associated with various cardiac abnormalities than on the basic theories of electrocardiography. If the student understood the electrocardiographic reflection of hemodynamics, he could approach the study of electrocardiography on a sounder footing, without needing to memorize complex variations associated with the various congenital lesions. Vectorcardiography, an aspect of electrocardiography that has become important recently, is omitted. The discussion of individual lesions includes some original and thought-provoking interpretations of electrocardiograms, particularly in relation to transposition of great vessels.

The chapters on cardiac catheterization and angiocardiography are amazingly complete, and methods of calculating hemodynamic data are presented well and in detail. The authors have assembled an accurate discussion of technics and methodology heretofore available only in multiple articles and journals. However, I would criticize the choice of peripheral dye-dilution curves to illustrate the diagnosis of intracardiac shunts. Dye injections in central sites are more accurate and have largely replaced peripheral injections.

The well-written discussion of embryology obviously reflects much research and thought. The portion on transposing the great vessels deals with this difficult subject in an understandable and logical manner.

A chapter is devoted to each of the congenital defects, with a complete discussion of incidence, etiology, pathology, hemodynamics, clinical features, electrocardiography, radiology, cardiac catheterization and angiocardiography. In each, the portion devoted to diagnosis reflects the vast experience of the authors and is particularly detailed in the discussion of differential diagnoses.

The common fault of medical textbooks is apparent in the discussion of treatment. In this rapidly changing field, it is almost impossible to write an up-to-date chapter on treatment. As one

(Continued on page A-144)

URINARY INFECTION PROVES CHRONIC:

Mandelamine is antibacterial, yet is not an antibiotic! Effective in many urinary tract infections resistant to antibiotics and sulfonamides, won't sensitize patients, no resistant strains develop. Mandelamine obviates need for alkalis or forcing of fluids, and it is excellent for long term therapy. Cost is low.

MANDELAMINE®

(BRAND OF METHENAMINE MANDELATE)

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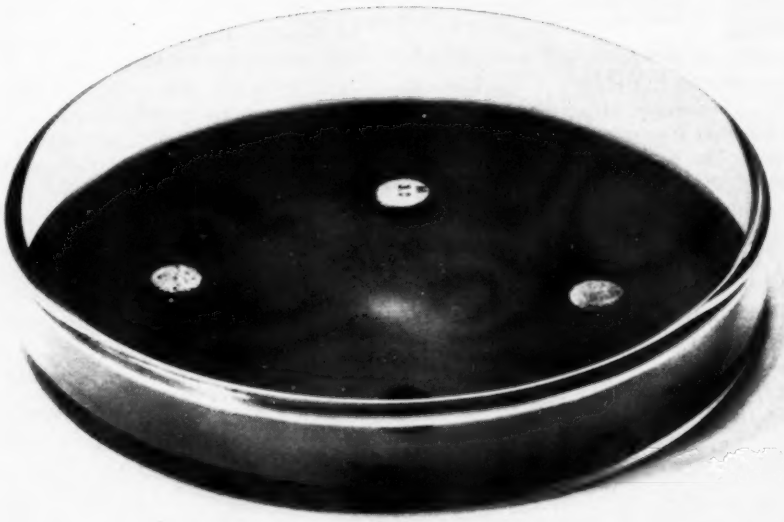


might expect, the mortality rates in open-heart operations are lower now than those quoted by the authors. With increased understanding of treating postoperative heart block, the statement that fatal termination is expected if the block is permanent is no longer necessarily true. I particularly like the common-sense approach to the indications for cardiac surgery.

Also discussed are the diagnosis, treatment and prognosis of rheumatic fever, rheumatic heart disease and heart disease associated with others of the collagen diseases, and the classification and treatment of cardiac arrhythmias, endocarditis, myocarditis and pericarditis.

The appendix contains a complete list of drugs and dosages useful in heart disease. However, the recommended digitalizing dose of 0.30 mg. DIGOXIN® per pound is obviously much too great. Personal communication from the authors proves this to be a typographic error; the correct dose of 0.03 mg. per pound is given elsewhere in the book. This technical error should not detract from the excellence of the work.

W. H. W.

► THE YEAR BOOK OF CANCER (1957-1958)

Compiled and edited by Randolph Lee Clark, Jr., M.D., Director and Surgeon-in-Chief, and Russell W. Cumley, Ph.D., Director of Publications, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston. 523 pages with 191 illustrations. 1958, The Year Book Publishers, Inc., Chicago. $8.00.

Reading original articles is the most fruitful way to obtain information from current publications, but when that involves reading 4000 articles a year, it is obviously impractical for a busy physician.

This volume answers the needs of doctors who wish to keep abreast of the current developments in the field of cancer, an area so broad in scope and principle that it envelops all specialties and subspecialties. The book consists of 235 articles selected by an editorial board of 124 physicians who have reviewed 4000 articles published in the last year in the United States and abroad. This was done in an attempt to present the best works on each facet of the cancer problem. From this Year Book the practicing physician will learn the progress that has been made, the treatment to recommend, and the cure rate and prognosis.

The subjects covered include: brain and nervous system; head and neck; skin; breast; chest; biliary tract, liver and pancreas; stomach, duodenum and small intestine; colon, rectum and anus; male and female genitourinary tracts; leukemias and lymphomas; tumors in pediatrics; the endocrine system; bone and soft tissue; pathology and cytology; radiotherapy; chemotherapy; reconstruction and rehabilitation; advanced tumors; epidemiology; chemistry; physics and radiobiology; genetics; bacteriology; virology; and animal tumors. Also included is a discussion on oncology in the Soviet Union.

Y. S.

► OCULAR ALLERGY

By Frederick H. Theodore, M.D., Associate Clinical Professor of Ophthalmology, New York University Post-Graduate Medical School, New York, and Abraham Schlossman, M.D., Clinical Assistant Professor of Ophthalmology, College of Medicine, State University of New York, Syracuse, New York. 420 pages, illustrated. 1958, The Williams & Wilkins Company, Baltimore. $12.00.

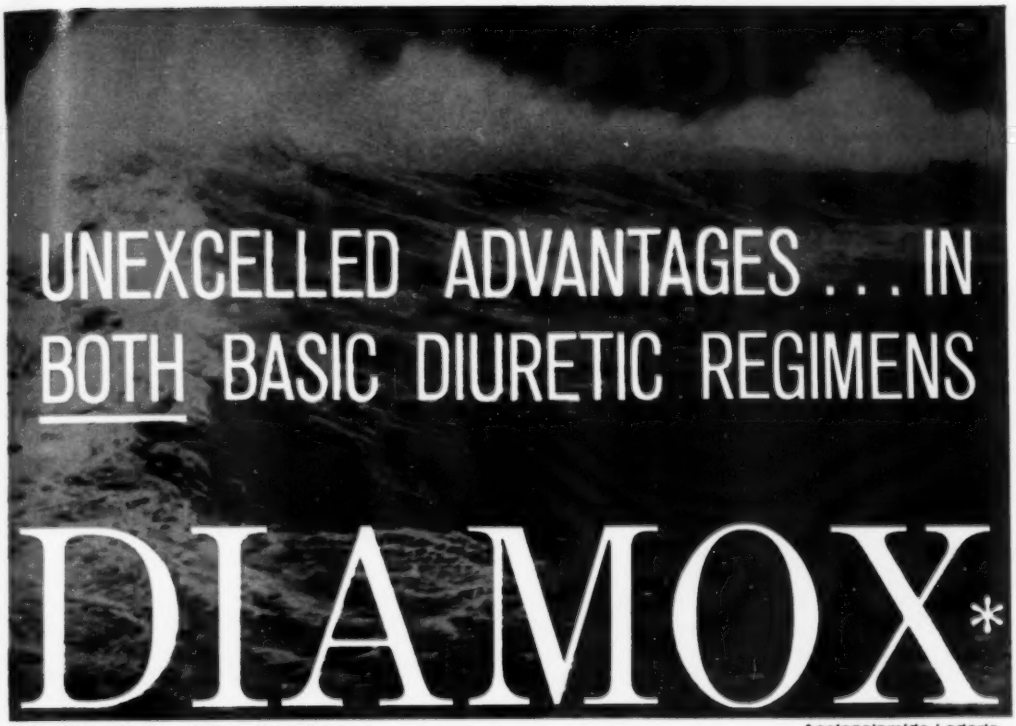
A comprehensive discussion of basic principles of allergy in general diagnosis, with emphasis on ophthalmologic application, sets the stage for a detailed description of eye diseases of allergic etiology. Allergic reactions must be defined and described and classified to make clear the writers' reference to "allergen," "antigen," "antibody," "anaphylaxis" and many other terms that have become identified with allergy.

The role of emotional status in allergic disease is recognized as a secondary factor influencing the degree of reaction in latent allergic states basically due to material antigens. However, a warning against complacency with a diagnosis of psychic disturbance as an initiating factor is followed by a plea to use all methods of examination, including skin tests with known antigens. So many are the possible variations in symptoms, so great the differences in response to tests, and so great the overlapping of diagnostic symptoms and reactions that often a definitive diagnosis is not possible.

The allergic diseases of the eye and the eyelids are discussed according to anatomic categories, beginning with conjunctiva and followed by eyelids, cornea, sclera, uvea, lens and optic nerve.

W. L. B.

(Continued on page A-146)



bicarbonate-regulating diuretic

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HOW DIURETICS ACT

Primarily by regulation of bicarbonate transport	DIAMOX acetazolamide
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1

Advantages of DIAMOX in single-drug diuresis

DIAMOX — operating through the well-understood mechanism of *bicarbonate* transport regulation—provides ample, prolonged diuresis in the great majority of patients.

DIAMOX is virtually nontoxic . . . has not caused renal or gastric irritation . . . has no pronounced effect on blood pressure. It is rapidly excreted, does not accumulate in the body, permits convenient dosage adjustment, allows unbroken sleep. Small, tasteless, easy-to-take tablets . . . usual dosage, only one a day.

- CARDIAC EDEMA
- PREMENSTRUAL TENSION
- EDEMA OF PREGNANCY
- OBESITY

2

Advantages of DIAMOX in intensive, two-drug diuresis

When intensive diuresis must be maintained, DIAMOX, alternated with an agent for regulation of *chloride* transport, has proved a regimen of choice. Through dual *bicarbonate-chloride* regulation, it produces maximal sodium-water excretion with minimal distortion of serum electrolyte patterns, greater patient comfort, lessened risk of induced drug resistance.

- ADVANCED CONGESTIVE HEART FAILURE
- REFRACTORY TOXEMIA OF PREGNANCY

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

Lederle

*Reg. U. S. Pat. Off.

► FRACTURES AND OTHER INJURIES

By members of the Fracture Clinic of the Massachusetts General Hospital and of the Faculty of the Harvard Medical School. Edited by Edwin F. Cave, M.D., Chief, Fracture Clinic, Massachusetts General Hospital, Boston. 863 pages with 607 illustrations. 1958, The Year Book Publishers, Inc., Chicago. $28.00.

An outgrowth of the very popular course in the treatment of fractures and other traumatic conditions which has been given at the Massachusetts General Hospital for more than 30 years, this book represents the work of 39 authors who have been instructors in the Fracture Clinic. It is excellently written and organized and deals with almost all types of injuries—their recognition and treatment, and the expected end results.

The organization of a fracture surface is discussed and should be helpful to those interested. Other chapters are devoted to the metabolic response to trauma, delayed union and nonunion, metabolic bone disease, pathologic fractures, early management of the acutely injured patient, the use and abuse of roentgenology, shock, anesthesia, rehabilitation, and thermal and blood vessel injuries. In addition, fractures are grouped concisely according to location; adequate discussions are given of the diagnosis, treatment and long-term management of fractures in general. In most instances more than one method of treatment is discussed and in every case these methods are clearly and adequately outlined.

E. W. J.

► A THERAPY FOR ANXIETY TENSION REACTIONS

By Gerhard B. Haugen, M.D., Assistant Clinical Professor of Psychiatry, Henry Hadley Dixon, M.D., Head, and Herman A. Dickel, M.D., Associate Clinical Professor, Department of Psychiatry, University of Oregon Medical School, Portland. 110 pages. 1958, The Macmillan Company, New York. $3.50.

The huge sale of sedatives and tranquilizers and the numerous articles concerning tension and anxiety states written for the laity and the medical profession attest to the proportion of these disorders in our society.

For years physicians have been seeking more efficient ways to manage these uncomfortable and sometimes disabling symptoms. The authors of this short monograph, who are psychiatrists in private practice, describe the method they have found most effective in dealing with anxiety states. That this therapy works best in their practice is perhaps the main point of the book, but they believe it is a simple method that any physician can employ quite readily. The publisher also notes that this book is so simply written that it will be of value to the layman.

The central thesis of the book is that the chronically anxious patient is in a state of chronic muscular tension, which is responsible for numerous somatic symptoms. The authors contend that teaching the patient to relax, using the technic described by Edmund Jacobson in "You Must Relax," releases the tension and relieves the patient of somatic symptoms. Perhaps this is an oversimplification, but it is the basic idea.

E. M. L.

► SKIN GRAFTING

By James Barrett Brown, M.D., Professor of Clinical Surgery, and Frank McDowell, M.D., Associate Professor of Clinical Surgery, Washington University School of Medicine, St. Louis. Ed. 3. 411 pages with 328 illustrations and six color plates. 1958, J. B. Lippincott Company, Philadelphia and Montreal. $15.00.

This handsome, well-illustrated and indexed volume presents multiple photographs of descriptive material drawn from the plastic surgical services of the authors.

The 35 chapters encompass general considerations and the early general and local care of burns, including a chapter on the early excision and grafting of some burns. The varieties of skin grafts, how to obtain and to apply them, and various types of pedicle flaps and the stages in the construction and application of such flaps are described. Contractures and the general principles of repair of contractures also are included. Chapters 15 through 27 are concerned with individual regions and the management of soft-tissue problems in these regions. The hands, axillae, arms and forearms, trunk, legs and feet, face, eyelids and orbits, nose, ears, neck and scalp all are discussed separately. Preoperative and postoperative photographs are shown.

J. K. M.

(Continued on page A-148)

Your difficult rheumatic patient...

on the job again

through effective relief and rehabilitation

For the patient who does not require steroids

PABALATE®

reciprocally acting nonsteroid antirheumatics . . . more effective than salicylate alone.

each enteric-coated tablet:

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► PEDIATRIC SURGERY

By Orvar Swenson, M.D., Professor of Pediatric Surgery, Tufts University School of Medicine, Boston. 740 pages with 980 illustrations. 1958, Appleton-Century-Crofts, Inc., New York. $20.00.

The specialty of pediatric surgery has followed the lead of pediatrics in recognizing that the medical problems of children differ extensively from those of adults. Since the pioneering leadership of Ladd 35 years ago, pediatric surgery has developed so that many conditions which previously were considered fatal are now successfully treated.

Most pediatric surgeons are primarily general surgeons who have attained special skill and experience in the management of surgical problems of children. The general surgeon is competent to carry out successfully many operative procedures on infants and children, yet there still remain enough complicated problems in this age group to tax the skill and proficiency of the pediatric surgeon who devotes full time to such problems.

Designed to supplement the standard volumes on general surgery, this book describes in detail features that distinguish a disease in children from that in adults. Many children's conditions not described in texts on general surgery are fully dealt with by the author. Preoperative and postoperative care and complications are presented in detail, and minor surgical procedures are included to aid the young surgeon. In addition, cystoscopic and bronchoscopic technics are given, and some consideration is afforded certain orthopedic and neurologic conditions and those involving plastic surgery.

S. D. M.

► REGIONAL ILEITIS

By Burrill B. Crohn, M.D., Consulting Gastroenterologist, and Harry Yarnis, M.D., Associate in Medicine for Gastroenterology, Mount Sinai Hospital, New York. Ed. 2. 239 pages with 81 illustrations. 1958, Grune & Stratton, Inc., New York and London. $7.25.

The senior author of this book was the first to describe the disease entity most commonly known as regional ileitis. Based on his experience with 676 cases of diverse types of ileitis, this monograph begins with an interesting account of the historical background and changing concepts of the disease. In the following discourse on the possible etiology many facets are considered, the final conclusion being that the true cause of ileitis is still unknown.

The gross pathology, clinical features and complications of regional ileitis are well described, and the section on roentgenographic manifestations is illustrated with 30 x-ray reproductions. Five major features in the step-by-step diagnosis of ileitis are presented in detail.

Discussions are included on both surgical and medical therapy. In the latter, a program emphasizing dietary management is outlined. Seven major indications and four major contraindications for surgery are considered, and the results obtained in 385 surgically treated patients are tabulated and classified. Short-circuiting operations were performed twice as often as resections and showed slightly better results; however, the authors do not strongly favor one method of surgery over the other.

New and original material is presented in an interesting and instructive section on malabsorption in ileitis. The closing chapters cover the prognosis and treatment of jejuno-ileitis and ileocolitis, which are less common forms.

Y. S.

► A MANUAL OF ELECTROTHERAPY

By Arthur L. Watkins, M.D., Assistant Clinical Professor of Medicine, Harvard Medical School, Boston. 259 pages with 167 illustrations and 34 tables. 1958, Lea & Febiger, Philadelphia. $5.00.

Electrotherapeutics and electrodiagnosis are discussed in this volume from the standpoint of their usefulness to students, therapists, physiatrists and all other physicians interested in the application of these procedures in diagnosis and treatment.

The introduction includes a discussion of physical forces and treatment and the history of physical therapy; it is followed by sections on heat and light, electricity, general electrotherapeutics and electrodiagnosis. It is unfortunate that the author devoted only six pages to ultrasonics, since expansion of this section would have been a valuable addition. The manual is well written in a very readable style, with understandable terminology. Numerous illustrations are included.

I. P. F.

(Continued on page A-150)

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1. Proctor, R. C., Southern Psychiatric Assoc. Meeting, October 7, 1957. 2. Feuss, C. D. and Gragg, L. Jr.: Dis. Nerv. Sys. *18*:29, 1957.

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► ANOMALIES OF INFANTS AND CHILDREN

By D. McCullagh Mayer, M.D., Associate Professor of Plastic Surgery, New York Medical College, New York, and Wilson A. Swanker, M.D., Professor of Plastic and Aesthetic Surgery, Ankara University Faculty of Medicine, Ankara, Turkey. 454 pages, illustrated. 1958, The Blakiston Division, McGraw-Hill Book Company, Inc., New York and London. $12.00.

Written primarily for the student and the general practitioner, this work is designed for ready reference in preparing them to discuss the cause and treatment of the anomaly with the parents. Both authors are experienced in dealing with many types of anomalies and have correlated their information in this book. The anomalies are considered on the basis of their relation to the body as a whole, as well as to the part involved. A general discussion on and a classification of congenital anomalies are offered; little space has been given to treatment technics which are covered in the standard textbooks on plastic surgery.

Exception might be taken to statements in the text that are at variance with commonly held opinions, particularly those given in the all-too-short chapter on cancer in children which, next to accidents, is the most frequent cause of death in childhood. A statement that there is no known treatment for leukemia and the failure to emphasize x-ray irradiation in managing Wilms' tumor and to suggest chemotherapy in treating cancer in childhood seem a gross oversight. In contrast, the space devoted to burns is long, as if the authors have had much personal experience in this field. Finally, using the body surface area to calculate fluid requirements in children has become more acceptable to pediatricians than using a percentage of adult fluid requirements.

S. D. M.

► PHYSICAL DIAGNOSIS

By F. Dennette Adams, M.D., Physician, Board of Consultation, Massachusetts General Hospital, Boston. Ed. 14. 926 pages, illustrated. 1958, The Williams & Wilkins Company, Baltimore. $12.00.

If Dr. Richard C. Cabot, the author of the first edition of this text, published in 1900, were alive he would be very proud of this edition. Extensive revisions and additions have been made since the last volume was published some years ago. On reading the present, well-illustrated edition, the physician will recognize that it is the work of an understanding and master clinician.

Beginning with a discussion of history and history taking, the author then covers physical examination in general. In the following chapter, he considers the body as a whole, beginning with a section on body stature. From this point, he adroitly proceeds to a discussion of the skin and then traverses the gamut of the entire body, from head to feet. He has not attempted to cover the entire field of medicine but wisely has presented those conditions which the practicing physician sees from day to day.

I. P. F.

► PATHOLOGY FOR THE PHYSICIAN

By William Boyd, M.D., Professor Emeritus of Pathology, University of Toronto, Ontario, Canada. Ed. 6. 900 pages with 489 illustrations, 12 in color. 1958, Lea & Febiger, Philadelphia. $17.50.

While this is the sixth edition of a treatise on pathology as applied to internal diseases, in many ways it is really a new book with a much better title. It has been written with the physician's needs in mind, and is a companion volume to the author's "Pathology for the Surgeon." It is not intended to be a textbook for medical students. In fact, this same versatile author has written one of the best textbooks of pathology for students.

This work represents a successful attempt to bring this book up to date. The text is most readable, with a readily useful arrangement of subjects presented in 20 chapters. Ample coverage is given to diseases of the heart, arteries, kidneys, respiratory system, stomach and duodenum, intestines, liver and gallbladder, pancreas, pituitary body, adrenal glands, thyroid, parathyroids, blood, spleen, lymph nodes and thymus gland, nervous system, and bones, joints and muscles and to the internal environment.

As the author says in the preface, "Modern medicine seems to have reached the logarithmic phase. In medicine as in 'Alice Through the Looking Glass,' it takes all the running you can do to keep in the same place. If you want to get somewhere else, you must run twice as fast."

A. H. S.

(Continued on page A-152)

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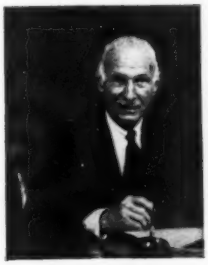

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► THE BRAIN AND HUMAN BEHAVIOR

Edited by Harry C. Solomon, M.D., Stanley Cobb, M.D. and Wilder Penfield, M.D. Proceedings of the Association for Research in Nervous and Mental Disease, December 1956. 564 pages with 200 illustrations and 53 tables. 1958, The Williams & Wilkins Company, Baltimore. $15.00.

A collection of papers selected from the 1956 meeting of the Association for Research in Nervous and Mental Disease, this volume takes its title from the theme of the program.

This is the twenty-sixth volume published by this organization over the past 36 years. Previous publications have dealt with research in varied fields, including epilepsy, schizophrenia, pain and tumors of the nervous system.

The book contains 21 chapters, none of which are necessarily related. The authors of the various chapters are some of the most noted men in the field of mind-brain research, and for the most part their papers are quite scholarly and highly theoretical.

Because of the technical and research-oriented nature of the discussions, this book would be of little value or interest to one outside the specific fields of neurophysiology, neuroanatomy, neurology, neurosurgery and psychiatry.

E. M. L.

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Books received are acknowledged in this department. As space permits, books of principal interest to our readers are reviewed more extensively.

Collected Papers of the Mayo Clinic and the Mayo Foundation. Vol. 49. 827 pages, illustrated. 1958, W. B. Saunders Company, Philadelphia and London. $13.00.

Speech Recovery After Total Laryngectomy. Part 1 by C. J. Hodson, F.R.C.P., Deputy Director of the Diagnostic Radiology Department, and part 2 by M. V. O. Oswald, F.C.S.T., late Chief Speech Therapist, University College Hospital, London, England. 36 pages, illustrated. 1958, The Williams & Wilkins Company, Baltimore. $1.50.

The Practical Use of the Microscope; Including Photomicrography. By George Herbert Needham, M.S., Lecturer in Microscopy and Photomicrography, University of California Medical School, San Francisco. 493 pages with 173 illustrations. 1958, Charles C Thomas, Springfield, Illinois. $15.50.

Human Blood in New York City. A study of its procurement, distribution and utilization. By the Committee on Public Health, The New York Academy of Medicine. 147 pages. 1958, The New York Academy of Medicine, New York.

The Psychology of Medical Practice. By Marc H. Hollender, M.D., Professor and Chairman, Department of Psychiatry, State University of New York, Upstate Medical Center, Syracuse. 276 pages. 1958, W. B. Saunders Company, Philadelphia and London. $6.50.

Doctors to the World. By Murray Morgan, Tacoma. 271 pages, illustrated. 1958, The Viking Press, Inc., New York. $5.00.

Essentials of Gynecology. By E. Stewart Taylor, M.D., Professor and Head, Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Denver. 502 pages with 343 illustrations, 4 in color. 1958, Lea & Febiger, Philadelphia. $12.00.

Religious Doctrine and Medical Practice. By Richard Thomas Barton, M.D., Associate Consultant, University of California, Los Angeles. 94 pages. 1958, Charles C Thomas, Springfield, Illinois. $3.75.

Simple Methods of Contraception. An assessment of their medical, moral and social implications. Edited by Winfield Best and Frederick S. Jaffe. 63 pages. 1958, Planned Parenthood Federation of America, New York.

Diseases of the Esophagus. By J. Terracol, Professor of the Faculty of Medicine of Montpellier, Montpellier, France, and Richard H. Sweet, Associate Clinical Professor of Surgery, Harvard Medical School, Boston. 682 pages with 409 illustrations. 1958, W. B. Saunders Company, Philadelphia and London. $20.00.

Bibliography of International Congresses of Medical Sciences. Prepared by W. J. Bishop. 238 pages. 1958, Charles C Thomas, Springfield, Illinois. $5.50.

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OCTOBER 1958

For The Doctor Whose Daughter Wants To Be A Nurse - here's a tax point to keep in mind. A full-time student nurse at an accredited school will spend some time in a hospital performing services as part of her training. While at the hospital, she will be furnished free room and board. Can the doctor still claim his daughter as a dependent during such period?

As a student nurse, the daughter would be in full-time attendance at an accredited school. Regardless of the daughter's age, the doctor, therefore, would be able to claim her as a dependent if he furnished her with more than half her support. In determining support, the Internal Revenue Service now states that the free room and board at the hospital may be ignored. That means that in the usual situation the doctor will be the sole support of his daughter during the training program and will be entitled to an exemption for her.

Are You The Family Doctor For This Family? - A young woman's husband died prematurely, leaving her with growing children to support on inadequate resources. Due to financial need, the talented widow has taken a good paying job. Her earnings now bar her from social security benefits based on her husband's prior employment. Do her small children also lose benefits as a result of her earnings?

There is a popular misconception. While her earnings bar her from social security benefits based on her husband's prior employment, her children do not lose out as a result. You might tell her that her growing children will still be entitled to benefits based on their father's employment, regardless of her current earning status.

If You Took A "Refresher" Course - this summer or expect to take one later in the year, your travel and living costs while away from home and fees for the course are deductible. Note this: To deduct fees and expenses directly related to the course, you must itemize deductions. You can't elect the optional standard deduction and take such expenses on your tax return. But you can deduct travel and living costs even if you elect the standard deduction and do not itemize your other deductions.

If Your Practice Is Still Growing - here's some tax record keeping advice. The individual who derives a substantial amount of income not subject to withholding is more likely to have his return selected for audit than the employe whose pay is subject to withholding. So the self-employed doctor falls within one of the professional groups most frequently subject to audit.

The Internal Revenue Service also is conducting an experiment with modern business machines. The experiment calls for machine processing of returns, with view to spotting those with deductions larger than normal considering income. Such returns would be selected for individual scrutiny, and if reviewing agent was still not satisfied, it would be followed by a full audit. If the experiment proves practical, it will soon be put into effect.

While this experiment is not directed specifically at the young doctor with income of $10,000 or under, he falls within one of the occupational groups most likely to be affected. He should be careful in retaining records of his deductions, particularly if they loom large in relationship to current income. Note that a return filed this coming April 15 will still be open for review and auditing in 1962.

* * * *

A Million Dollar Insurance Policy On His Wife - was taken out recently by a wealthy man. Why such substantial insurance coverage? Probably because the husband's estate plan was based on the assumption that his wife would survive him, and such planning can cause tax complications if she predeceases her husband.

To reduce his taxable estate and minimize estate tax on his death, the husband had been making sizeable gifts to his wife. Because of the gifts, there would be an estate tax due on the wife's death. By purchasing insurance on his wife's life and giving the policy to the children, the children would receive face value of the policy, free of income and estate taxes, if wife predeceased her husband. They would have in their hands liquid funds which could be used to pay estate taxes. It would not be necessary to make a forced sale of any assets in the wife's estate to secure cash to pay estate tax.

This is a large-scale example of how insurance can be used in estate planning. But insurance has other valid uses in the family planning field on a smaller scale.

The Doctor Might Check His Insurance Program - in light of new types of policies being issued which offer greater flexibility in family planning with increased tax shelter. Here are some examples.

(1) Family Protection Policy: Under this type of policy, the doctor's wife is also insured for a lesser amount under a rider when the doctor takes out insurance. For the younger doctor, it offers financial protection if his wife dies prematurely. Immediately after such

premature death, the young doctor will be faced with added family living costs, e.g., increased child care expenses, perhaps even boarding school costs. Insurance on his wife will not lessen the doctor's personal loss, but the income tax-free insurance recovery will ease the burden of added family expenses.

(2) Premium Cost Reduction: Premiums paid by the doctor on his life insurance are personal expenses and do not give a tax deduction. That means that premium payments must come out of his after-tax income. Any reduction in premium cost, therefore, means an after-tax saving. More and more companies are issuing policies which cut premium cost on larger policies. Per dollar, the premium rate is reduced as the doctor increases the amount of his insurance.

(3) Increasing Insurance Coverage: Many a young doctor finds his income, after taxes and living costs, does not permit him to buy all the insurance he currently wants. To protect his family, he will increase coverage later when his income increases. But he worries that an intervening disability (before his income allows him to increase coverage) might make him uninsurable, except at premium rates. At a small increase in current premium, some companies now issue policies which allow insured to increase coverage substantially at a later date without a physical examination, if additional coverage is elected within certain periods of time.

* * * *

Does Stock Investment Protect Against Inflation? - Many astute market observers believe that recovery in stock prices in 1958 from 1957 lows is largely due to investors seeking protection against inflation. Stock investment does offer protection against continued loss of the dollar's purchasing power. But there is considerable difference of opinion as to extent stock investment protects against inflation. One brokerage house surveyed the period between 1939 and 1957 with breakdowns for shorter intervening periods.

Over the full period starting with 1939 and ending with last year, stock investment gave ample protection against inflation. During this period the cost of living rose 104%. During the same period, an investment in a diversified portfolio of common stocks would have shown an increase of 231%. If investment had been limited to stocks in non-durable goods companies, increase in value would have averaged 451%; in durable goods manufacturing 291%; and in all other industries, with the exception of utilities, stock value increases would have exceeded rise in cost of living. If investment was limited to stocks of sound utilities, the cost of living rise would have exceeded stock price increase -- 104% to 56%.

For the shorter 1939-1948 period, the figures are not as favorable. For instance, an investment in a diversified portfolio of common stocks would have shown an average price increase of 32%.

In the same period, the cost of living rose 73%, but that period covered World War II and the post-war adjustment. Even so, as the cost of living rose so did stock prices, although not at the same rate. For subsequent periods stock prices rose faster than the cost of living. In the 1948-1951 period, the cost of living rose 8%, a diversified portfolio of common stocks, 40%. In the 1951-1957 period cost of living again rose 8%, common stock portfolio almost 80%.

In recent months, greatest stock market activity has centered around the low-priced shares of new and relatively untried companies. Don't rely too much on past market history to justify such investment as an inflation hedge. The statistics which would indicate that diversified stock investments do protect the investor against inflation largely reflect investment in moderate to higher priced shares of sound, long-established companies. Even such investment is not the perfect inflation hedge if investor is forced to realize on investment during period when cost of living is rising at an accelerated pace. For instance, stock investment would furnish some protection even during the 1939-1948 period. Then both the cost of living and stock prices rose, but the former at a more rapid rate than the latter.

* * * *

The Doctor's Recommendation Carries Weight - with the tax authorities. The recommendation may permit the patient to get a tax deduction for a medical expense which otherwise would not be allowed. Here are two more examples.

(1) A wife-mother was recuperating at home from a serious illness. During the period of convalescence she would need some nursing aid and someone to care for the children. Normally, pay of a domestic for such services would not qualify in any degree as a medical expense. The Internal Revenue Service, even under these circumstances, generally will not allow a deduction for child care expenses. That's so even though rest and quiet are essential to the health of the mother. But one doctor was able to convert a non-deductible expenditure to a deductible one in part. He recommended that a woman be hired with some nursing ability, specifically a practical nurse, to assist the wife and care for the children.

Under those circumstances, the Treasury conceded that part of the salary paid such woman qualifies as a medical expense. An allocation of her salary could be made for nursing duties she performs, and to that extent, husband-father is allowed a medical deduction.

(2) Costs incurred in the purchase of vitamins normally are not deductible as medical expenses. Such costs usually are considered in the same category as cosmetics, toothpaste, mouthwash, etc. But one local office of the Internal Revenue Service (Detroit) has conceded a deduction may be allowed. Where vitamins are taken as a substitute for food or beverage solely to satisfy one's nutritional requirements, there is no deduction. But where they are prescribed by a doctor as an addition to diet for health purposes, a deduction will be allowed.

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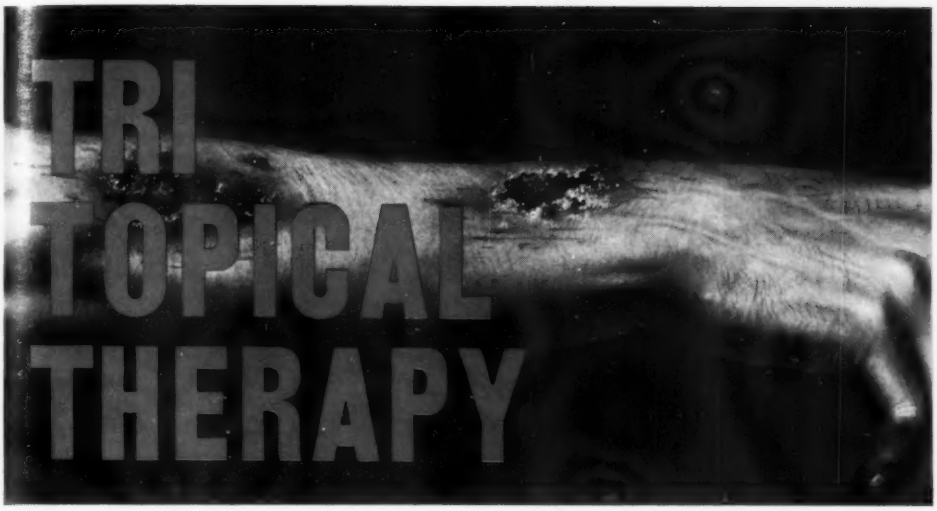

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DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

July 28—By plane to New York, leaving Chicago at 5 P.M. and arriving in Philadelphia at midnight, after circling La Guardia, Idlewild and Newark and going part way to Baltimore. So hired a limousine, sharing with six other passengers, including Friedman, lawyer for the Yankees, a professor of physics, and two students, and reached New York at 3 A.M.

July 29—For a conference with Runyon and Beebe; then to Howard Rusk's institute for luncheon with Billy Reynolds, Ed Pool, Niklas and Lynch and to talk about plastics. Thereafter to visit Herbert Mayes, and then came Mark Soroko, Doris and Rose and Sam Horowitz to dine at the Black Angus and to try some mathematics.

July 30—For breakfast came Larry Salter, talking of medical journalism and public relations. Then to confer with Stanley Lasdon about publicity. At noon to luncheon with the Rusks, Bernard Gimbels, Covalt, Rotbart and Lowman and to meet George Deaver and to see the new additions to the amazing Institute of Rehabilitation. In the afternoon to see the lovely new homes of Paul Warwick and Henry Legler, and for a late conference came Niklas, Lynch and Straub. Later with Mel and Polly Evans and daughter to dine at the Gold Coin, a Chinese restaurant serving delicious food, meeting Morris F. Friedell, who journeyed in from Bell Laboratories in Murray Hill, New Jersey. Then all to visit Herbert Mayes, greeting Grace and Vicky and Alex, and played at bridge with George Marek and Muriel and Herr Stepanek in a game in which every hand was a delight until Herbie, who had been wailing, suddenly climaxed it all with a small slam following some intellectual bidding.

July 31—To breakfast with Stan Henwood and then to see Bill Pennock presiding over the Hudnut offices. Next, a brilliant meeting for the final steps on *World-Wide Abstracts of General Medicine* with Bill and Stanley Lasdon, Len Scheele, Paul Robinson, Elwood Douglass and Collter. For lunch came Attorney Clifton Cooper and staff to prepare some documents, and then came Mel Evans. So home again on the 5 o'clock Flagship, coming in right on time, and read en route the autobiography of the analyst Reik, "Seeing With the Third Eye."

Aug. 1—Clearing the desk for Z.W.H.'s departure, discussing arthritis with Edmund Jacobson and Johnny Mirt, and surgical affairs with Max Thorek.

Aug. 2—Reading Bates' "The Darling Buds of May," full of delightful humor of the English countryside and an income tax investigator and an old man who finds life "perfick." Then saw the White Sox lose to the Yankees, which gets tiresome, and read Motley's "Let No Man Write My Epitaph," taken from the famous poem by Southey.

Aug. 3—To play at golf and dined with a large group of young golfers.

Aug. 4—At the desk working on abstracts and entertaining four grandchildren.

Aug. 5—At noon to Ravisloe, conquering Maurice Goldblatt at golf, though he is still improving, and then was devastated in mathematics, where he needs no improvement.

Aug. 6—To the station to see Friedell off for Rochester. The house being filled with decorators, departed for luncheon with Dr. Thompson, who edits *Endocrinology* and *Geriatrics*. Then to the Museum of Science and Industry with all the small fry and met Major Lohr, who should have done the Brussels Fair.

Aug. 7—To play golf in the afternoon with Altheimer, Boas and Maurice and ended with a 22 ft. putt that compensated for all the previous difficulties.

Aug. 8—Mistress Pepys falls ill with a respiratory virus so the small fry depart. At noon to lunch with Russ Stewart at the *Sun-Times* and discussed business and biology at the round table.

Aug. 9—With Mistress Pepys, who convalesces. Read also a new novel by Simenon, which is a typical story of French marital and "immarital" living; also read "The End of the Road," by John Barth, which is an extraordinary story of a mentally disturbed grammar teacher, ending with the most horrible account of a quack's doing an abortion that I have ever seen in print.

Aug. 10—At the desk, simul-

(Continued on page A-214)

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taneously watching the erratic Cubs fumbling away a ball game. In the afternoon to a party given by the Joselits, whose son undertakes marriage, and also to call on Ted Vatz, who is up and about after what is called a minor coronary.

Aug. 11—Busy with preparations to inaugurate *World-Wide Abstracts of General Medicine.* Reading now Llewellyn's "Chez Pavan," which is a novel of life in a hotel which could well be the Ritz in Paris.

Aug. 12—To play at golf and gin in the afternoon and evening.

Aug. 13—Again at my toil and read all the medical periodicals and also a story of the Basuto in Africa called "The Blanket," which carried me back to the days when I studied anthropology with Frederick Starr.

Aug. 14—To Ravisloe for more golf, improving slowly, and more mathematics, improving immensely.

Aug. 15—What a blessing is the long-distance telephone, which saves more hours than almost any other time-saving device.

Aug. 16—Saw on television the immensely improved White Sox defeat Cleveland. In the evening to dine with Frank and Antoinette Pope, who make food that looks and tastes delicious and kills you with calories.

Aug. 17—To play at golf with Leterman, Friedell and Levin, and was impossibly bad because I could not keep the left arm straight. At night to dine sumptuously with Charles Wilinsky and his lovely Lily, and met my alert publisher, Teresa Cohen, who was conducting six other ladies into the miracles of Chicago. So played at mathematics with Charles, Friedell and Dry, and still lucky.

Aug. 18—Z. W. H. being returned from her holidays, tanned and some pounds heavier, began with a mass of delayed correspondence and other production. Teresa Cohen came to luncheon and for an editorial conference. At night to Camelia House at the Drake with Miklos Sperling, Straub, Hoge and Friedell to talk of new plastic devices. The dinner and conversation of two hours was different from any drug, being both relaxing and stimulating.

Aug. 19—At the desk, at Ravisloe, and at the Kungsholm, where Charles Haney entertained the hospital administrators. What a nice, versatile day! Here were all the Haneys and, from Corning, Martha Iver and McMillan from Alton and Grady Hatton from Salisbury, Maryland, and many, many more.

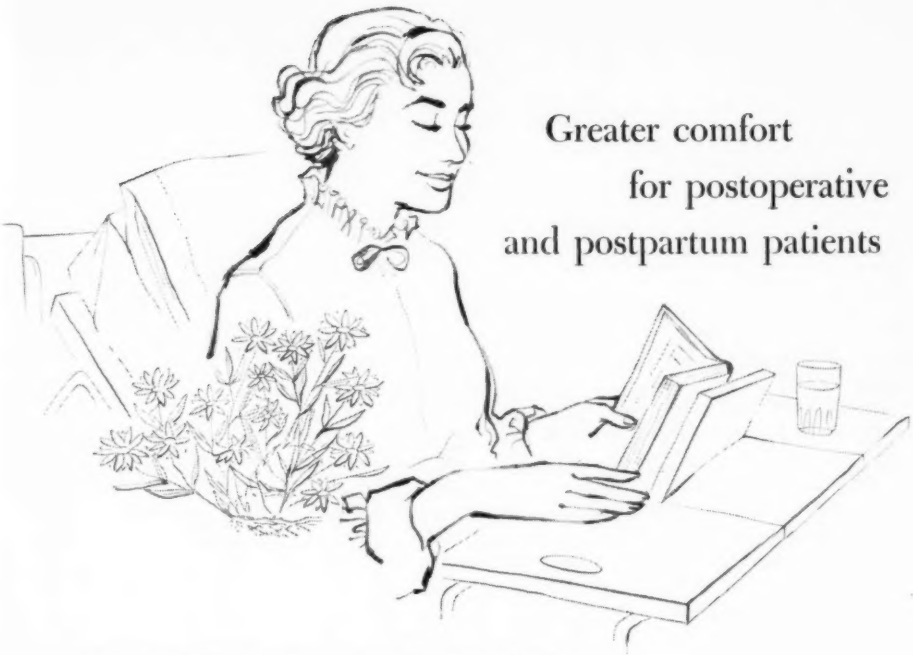
Aug. 20—Rosemary Friedell had a birthday and all the little ones helped her celebrate.

Aug. 21—At noon came the Sorokos of Revlon and the afternoon and evening filled with entertaining and a mathematical misfortune. Reading also two fine mystery tales, "The Eighth Mrs. Bluebeard," by Hilary Waugh, which is a beautifully designed mystery series of murders, and a terrific East-West German border story by Manning Coles called "No Entry." Paul Robinson came for the final touches on *World-Wide Abstracts of General Medicine,* and these little details make a great difference in ultimate success.

Aug. 22—Again with Robinson. In the evening with all the family and Teresa Cohen, Paul Robinson, Soroko, Cornbleet and Rattner to the Congress for a great dinner honoring Bob Hope. Here were Jack Benny, George Halas, Kupcinet, Russ Stewart, Mayor Daley and all the La Rabida trustees. The Variety Club made a presentation, and the fun was fast and furious. Zsa Zsa Gabor beamed and Joey Adams and Al Kelly convulsed the listeners. But the newest and best tale among hundreds came from Halas. In a game between the Cardinals and Bears a fullback charged into the Bear line; his left leg was seized by one giant guard, his right leg by the other guard, a rookie. They lifted the fullback high in the air. As they held him immovable, the veteran guard turned to the rookie and said: "Do you want to make a wish?"

Aug. 23—To play at golf with Gene Falstein, the psychoanalyst, and the air was filled with the jargon of aggressions, guilt feelings, projections, death wishes and what not. In bridge made a grand slam against Chester Buchsbaum, who is a bridge "necropsist," doing an autopsy on every hand. So dined well with the Feiwells, Pearlmans and Mort Weisses and rode home late well content. Before falling asleep read some trenchant essays of Roger Lee, "A Doctor Speaks His Mind." His medical heroes are Herbert C. Moffett, San Francisco, Frank Billings, Chicago, George W. Crile, Cleveland, and the Mayo brothers. Add to these from abroad Sir James Mackenzie, Sigmund Freud, Jung, Janet and Pavlov. He also mentions many more of the illustrious names of the past.

(Continued on page A-216)



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Aug. 24—To the Club, playing well at golf but in a steady slump in mathematics.

Aug. 25—All day at the desk. Ken Arnolt came to talk of new technics of binding.

Aug. 26—Early came Sylvia Covet for four hours of conferences on POSTGRADUATE MEDICINE and some grand plans for future issues. In the evening with the Feiwells to the Blackstone, where a great crowd assembled at a dinner given by the Friends for his birthday, which they called "Friendly Persuasion." Here chatting with many who came from all the suburbs, dining wonderfully, and dancing enough to shake loose the aging joints.

Aug. 27—In the morning came John Baruch, flying in from New Jersey, to talk of publicity and public relations. In the afternoon a committee of 11 to plan a great affair for the City of Hope. Here were Mages, Francois Pope, Weinstein and many others. In the evening Justin and Ann to dine and to confer and thus passed the day like a shadow, with so much to be done. So before going to bed finished Mary Renault's "The King Must Die," which is the legend of Theseus and the Minotaur, magnificently told and more exciting than the tales of the bull ring in Spain.

Aug. 28—Once more striving to bring the work abreast of the day. In between medical journals and my scrivening and editing, read "The Young Caesar," by Rex Warner, which tells once more in fascinating prose in the first person the growth and maturity of Julius Caesar.

Aug. 29—A visit from Joe and Minnie Kirsner, who are completing their vacation, bringing highly educational pictures about ulcerative colitis. Read also "Sidelights on the History of Medicine," edited by Zachary Cope, in which many of England's elite in the medical profession express their views of medicine's progress. The day hot and humid with the worst of Chicago's summer weather, so in the evening triumphed at last over Albert with seven straight victories altogether.

Aug. 30—Cleaned the desk and played at golf and took the Friedells to Morton's for a farewell dinner.

Aug. 31—The American Legionnaires parade with whistles and horns. So took off again for golf and gin with Franklin Kahn against two opponents, and we did well in a set game.

The Medical Muse

RICHARD ARMOUR

JUST A SECOND

The doctor, who drives much and far,
Requires, of course, a second car.
One car his wife must have to market.
She needs to drive it and to park it.
The other he must have to go
On calls that take him to and fro.

A second car there is, you see,
In what's a two car family,
One car for him, one for his wife. . . .
And sometimes there's a bit of strife
Re whose is which. May I suggest
I know whose car is second best.

OLD NURSE AND NEW

The old nurse knew the patients' names,
Knew Mrs. Jones from Mrs. James,
Knew who had children, knew their ills,
Knew also who could pay their bills.

The old nurse knew the salesmen's quirks,
Knew how to usher out the jerks,
Knew where to find, with eagle eyes,
The tucked away, half-hid supplies.

The new nurse—here's the rub, the sting—
The new nurse doesn't know a thing.
But give her time, she'll know by heart
The ins and outs—and then depart.